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APRIL 1956
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Idiopathic Hyperlipemia Associated with Coronary Atherosclerosis
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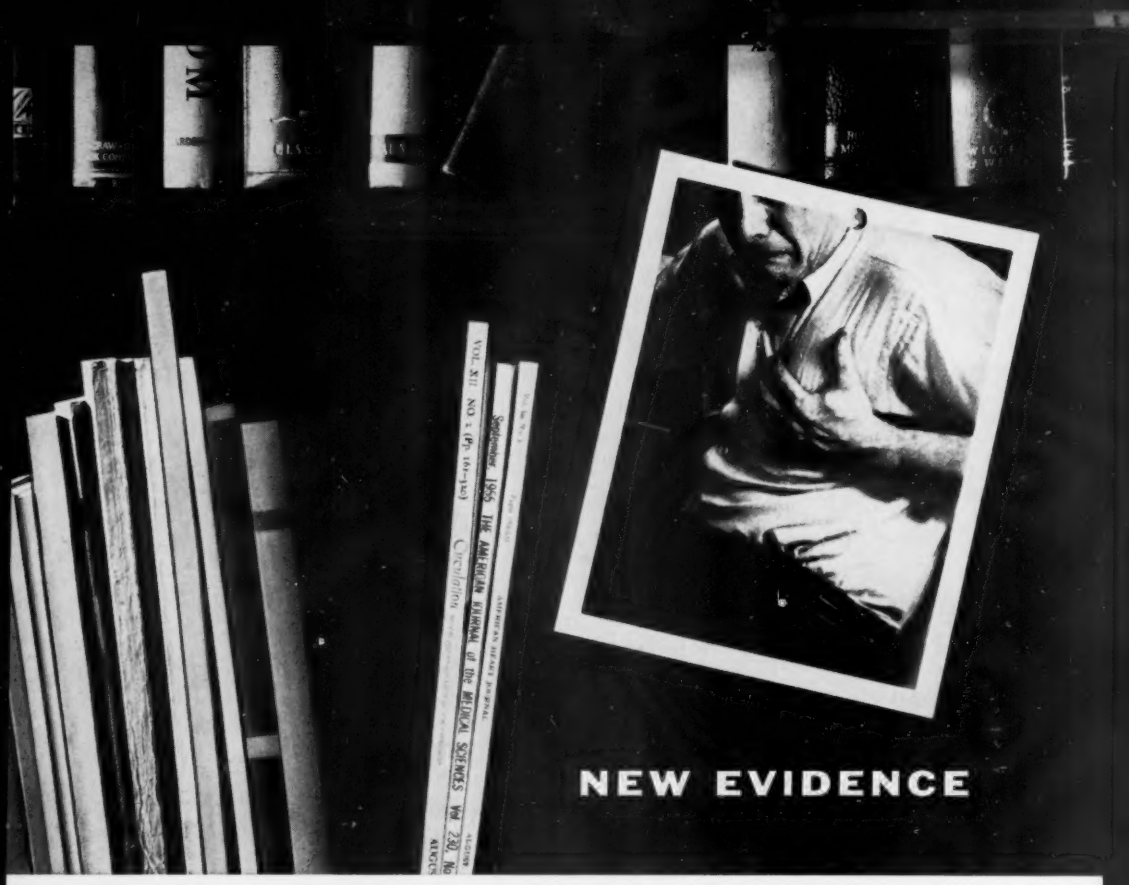

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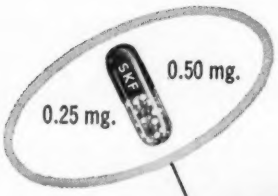

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Calories	379	13

*Berryman, G. H.: Obesity—A Brief Review of the Problem, Metabolism 3:544 (Nov.) 1954.

**Percentages of daily allowances for fairly active man 45 years of age, 67 inches in height, and weighing 143 pounds: Recommended Dietary Allowances, Washington, D.C., National Academy of Sciences—National Research Council Publication 302, 1953.

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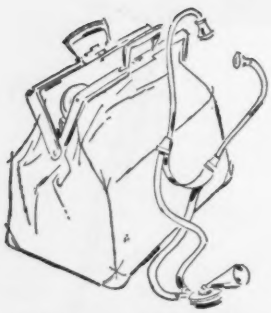

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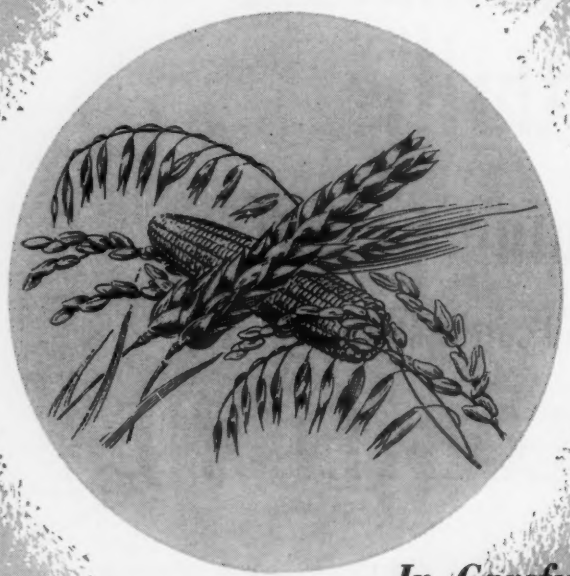
Effect of Breakfast and Source of Protein on Blood Sugar Level of Patients with Diabetes



In Carefully Controlled Laboratory Studies . . .

Although many changes have been brought about by its discovery, insulin has by no means solved all the problems of diabetes or obviated the need for further study and application of dietary treatment. After years of trial and error, the diet for the person with diabetes is now essentially that of a normal person. In a carefully controlled study conducted jointly by the Departments of Nutrition and Physiology at a distinguished medical school an experiment was designed (a) to determine the effect that breakfast, supplying one-third of the total daily caloric allowance, had on the blood sugar level of the diabetic patients receiving NPH insulin, and (b) to compare the effects of breakfasts in which the protein was entirely of animal origin with those in which the protein was entirely of plant origin.

Summary and Conclusions

Fasting blood sugar levels and levels obtained every ½ hour for 3½ hours from twelve patients with diabetes maintained on NPH insulin were compared following the consumption of two experimental breakfasts, one containing 25 gm. protein from animal sources and the other containing the same amount of protein, but of plant origin. The data justify the following conclusions:

The animal and plant protein were equally effective in maintaining the blood sugar above the fasting level following breakfast.

Twenty-five gm. of either animal or plant protein were adequate to maintain the blood sugar significantly above the fasting level for a period of 2½ hours, and to prevent it from falling below the fasting level for at least 3½ hours.

It is of no consequence as to whether the protein in the diet of the person with diabetes is of plant or animal origin, since the blood sugar levels behave almost identically following the ingestion of the two kinds of protein.

Zickefoose, Joan, Hardin, Robert C., Tuttle, W. W., Daum, Kate, and Salzano, John: *Effect of Breakfast and Source of Protein on Blood Sugar Level of Patients with Diabetes.* J. Am. Dietet. A. 31:1016 (Oct.) 1955.

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Furlong, J. J.: California Med. 81:297 (Nov.) 1954.

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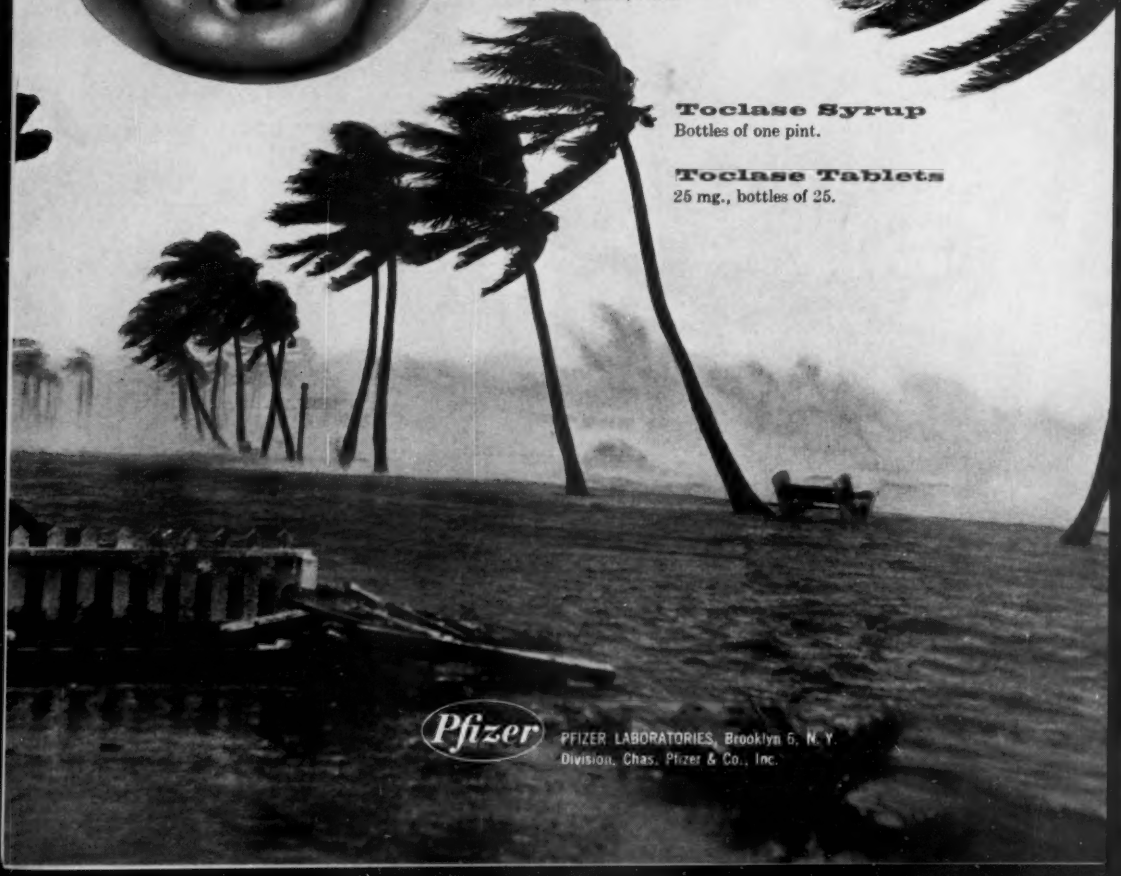

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A.M.A. Archives OF INTERNAL MEDICINE

Hyperthyroidism Treated with Radioiodine

A Seven-Year Experience

WILLIAM H. BEIERWALTES, M.D.
and
PHILIP C. JOHNSON, M.D., Ann Arbor, Mich.

More than 14 years have elapsed since Hertz [1] and Hamilton [2] first used radioiodine to treat thyroid disease. During this time reports [3] have been published on the treatment of more than 1700 hyperthyroid patients with radioactive iodine, I^{130} and I^{131}. Yet many questions remain unanswered. Does radioiodine, I^{131}, cause cancer of the thyroid gland 10 to 20 years after a dose of I^{131} is given for the treatment hyperthyroidism? [4] Should one aim to "cure" the hyperthyroidism with one dose, or should multiple small doses be used to avoid a high incidence of hypothyroidism? Do severely hyperthyroid persons with an unusually high I^{131} uptake require a smaller or larger dose of radioiodine than the average patient? [5] Should radioiodine be used as preoperative preparation for toxic nodular goiters? * Will a substernal goiter disappear by the time I^{131} therapy has rid the patient of thyrotoxicosis? Is the I^{131} method of relieving thyrotoxicosis accompanied by a lower incidence of progressive exophthalmos than is found after surgical subtotal thyroidectomy? [6]

We can not give a definite answer to these questions, but this review was made of our seven-year experience with the primary intent of shedding further light on these and other similar important considerations before more hyperthyroid patients were treated with I^{131}.

METHOD AND MATERIAL

Three hundred thirty patients were given one or more treatment doses of I^{131} from Feb. 24, 1948, to Jan. 1, 1955. One of us (W. H. B.) examined every patient. All patients were referred to University Hospital, usually from cities distant from Ann Arbor. No euthyroid patient is included in this report who was given a dose of I^{131} for the purpose of inducing a medical thyroidectomy for heart disease, Parkinsonism, pulmonary emphysema, or a nontoxic large goiter. The indications for I^{131} treatment in this series of patients were exophthalmic goiter in persons over 40 years of age or exophthalmic goiter patients under 40 who had a previous thyroidectomy with persistence or recurrence of the thyrotoxicosis, refusal of operation by the surgeon or the patient, inadequate preoperative preparation because of intolerance to antithyroid drugs, preoperative preparation requiring more than six months, or progressive exophthalmos. All patients had symptoms and/or signs of thyrotoxicosis. No patient was treated solely because of an abnormal value disclosed by one laboratory test. If the patient was taking strong iodine solution U. S. P. (Lugol's solution), this medication was stopped until the I^{131} uptake test showed a hyperthyroid curve. Antithyroid drugs were stopped at least two days before a treatment dose was given. Neither iodine nor antithyroid compounds were given to control thyrotoxicosis after a treatment dose of I^{131}. If the patient was

Received for publication Oct. 6, 1955.

From the Department of Internal Medicine, University of Michigan Medical School.

The expense of this study was defrayed in part by grants from the Michigan Memorial Phoenix Project.

* Crispell, K. R.; Parson, W.; Hollifield, G. F., and Aldrich, E. M.: The Use of Radioactive Iodine to Prepare Patients with Toxic Nodular Goiter for Surgery, read before the American Goiter Association, Oklahoma City, April 28, 1955.

judged to be too sick from his thyrotoxicosis to easily withstand abstinence from antithyroid drugs for two months after I^{131} treatment or the added metabolic burden of the effects of stored thyroid hormone dumped into the circulation as a result of thyroiditis, his thyrotoxicosis was brought under good control with antithyroid medication before I^{131} was administered. Patients with congestive heart failure complicating thyrotoxicosis were hospitalized and treated energetically for congestive heart failure before treatment with radioiodine. A few elderly and malnourished persons with heart disease were urged to sharply limit their physical activity for one month after treatment. All other patients were allowed to carry on normal lives after I^{131} was administered. All patients were warned of the possibility that they might develop symptoms of irradiation thyroiditis, worsening of their thyrotoxicosis, or hypothyroidism and that they would probably show no improvement for one to two months after treatment.

The dose was decided empirically upon the basis of estimated gland size, severity of thyrotoxicosis or per cent of administered tracer dose of I^{131} found in the thyroid at 24 hours, and the general clinical condition of the patient. Goiters were recorded as being 1+ to 4+ in size. A thyroid gland just visibly and palpably enlarged was judged to be a 1+ goiter. A 2+ thyroid enlargement was judged to be the size of the average exophthalmic goiter in this area, usually about 35 to 55 gm. Four plus was recorded when the goiter extended more or less directly from the suprasternal notch and clavicles to the mandible. These goiters were always more than 200 gm. "Nodular goiter" was recorded when one or more hard nodules were visible and palpable and more than 1 cm. in diameter. The majority of these patients were judged to have true adenomas, but undoubtedly many had adenomatous goiter nodules.[7] Patients with an "average" degree of thyrotoxicosis usually had basal metabolic rates between +25% and +50%. The 24-hour I^{131} uptake test in such patients usually ranged from 55% to 75%. The dose of radioiodine was estimated during the last five years of this study according to the following plan. It was judged that the average dose used to treat the patient with average size exophthalmic goiter with thyrotoxicosis of average severity was about 10 mc., when an attempt was made to "cure" the patient with one dose of I^{131}. The dosage was increased or decreased 1 to 3 mc. from this figure of 10 mc. according to increased or decreased estimated size of thyroid gland as compared with the "average" exophthalmic goiter. An additional consideration was the degree of activity of the thyroid gland. If the toxic goiter was judged to be more active than the average exophthalmic goiter, the trend was to decrease the dose below 10 mc., on the basis that in this instance a higher per cent of the dose would be concentrated by the thyroid gland and consequently more irradiation would be delivered to the thyroid.

Hertel exophthalmometer measurements were performed upon many patients who had no apparent exophthalmos, but a fairly successful attempt was made to perform eye measurements upon every patient who had suggestive evidence of true exophthalmos. These measurements were performed by the department of ophthalmology (Dr. Bruce Fralick, Chairman) at the time of the initial treatment dose and at the three- and six-month return visits.

Each patient was asked to return in three months to check on the completeness of the response of his thyrotoxicosis to treatment. Eighty-seven per cent of all patients treated had returned for follow-up at the time of this review (Jan. 1, 1955). Twenty-four patients had been treated too recently to be reevaluated. Patients or their physicians were contacted by letter for follow-up if the patients did not return at three months for their check-up.

Of the total of 330 patients treated, 82 patients were judged to have nodular goiters. In other words, the ratio of exophthalmic goiter to adenomatous goiter patients was 3:1. The sex ratio in both exophthalmic and adenomatous goiter groups was approximately four women to each man. The number of patients treated in each decade of life

TABLE 1.—*Age of Patients in Decade Distribution*

Age, Yr.	Patients, No.	
	Nodular Goiters	Non-Nodular Goiters
10-20	0	11
20-30	2	**29**
30-40	3	**64**
40-50	17	66
50-60	17	50
60-70	**29**	21
70-80	12	5
80-90	2	2

TABLE 2.—*Yearly Percentage Distribution of Patients with Thyrotoxicosis Treated with I^{131} (1948-1954)*

	82 Nodular Goiters, % of Total	248 Non-Nodular Goiters, % of Total
1948	4	0.4
1949	1	2.8
1950	7	6
1951	10	7.8
1952	18	23
1953	26	27
1954	34	33

from 10 to 90 years is shown in Table 1 for patients with nodular and non-nodular goiters. It is evident that our patients with nodular goiters were generally older than patients with non-nodular goiters. Table 2 presents the numerical distribution of patients treated in each of the seven years covered by this study. An increased number of patients each year have been treated with I^{131}. The rapid increase in number of patients with nodular goiters treated is due in part to the fact that I^{131} more and more frequently is used to prepare patients with toxic nodular goiter for thyroidectomy. Not infrequently, when the patient has been made euthyroid his nodular goiter has disappeared and no thyroidectomy is performed.

usually longer than six months. Of exophthalmic goiter patients, however, 32% were treated because they had had a previous thyroidectomy and now suffered from persistence or recurrence of their thyrotoxicosis. Twenty-seven per cent of exophthalmic goiter patients were treated with I^{131} as the treatment of choice in persons over 40 years of age. Other points of interest noteworthy in Table 3 are the 4% to 5% incidence of intolerance to iodine and antithyroid medication, the 6% to 13% incidence of progressive

TABLE 3.—*Principal Reason for I^{131} Treatment*

	Patients with Nodular Goiter		Patients with Non-Nodular Goiter	
	No.	% of Total	No.	% of Total
Previous thyroidectomy	19	23	79	**32**
Surgery refused by patient or surgeon	13	**58**	14	6
Over 40 yr. of age	0	..	66	**27**
Drug reaction	3	4	13	5
Serious eye signs	5	6	31	13
Decreased life expectancy	14	17	10	4
Preoperative preparation taking longer than 4 mo.	28	**34**	35	14

RESULTS AND DISCUSSION

1. Principal Reason for Treatment with Radioiodine

Table 3 presents a breakdown of the principal reasons for I^{131} treatment in our patients. The majority of patients with nodular goiter were treated with I^{131} because subtotal thyroidectomy was refused by the surgeon or by the patient. The next commonest cause for the use of I^{131} in patients with toxic nodular goiter was preoperative preparation taking longer than four months, exophthalmos, and the 34% to 14% incidence of inadequate preoperative preparation after four months of treatment with iodine and antithyroid medication. It is important to realize that these figures present a distorted incidence of complications encountered in the treatment for thyrotoxicosis, because an effort was made to select just such patients for I^{131} therapy. Included in the category of "decreased life expectancy" (Table 3) are patients with carcinoma of the breast with metastases, lymphosarcoma, advanced arteriosclerotic heart disease, and others.

TABLE 4.—*Size of Initial Dose*

	Initial Dose, Av., Mc.	
	Nodular Goiters	Non-Nodular Goiters
1948	6	4
1949	8	11
1950	11	11
1951	12	10
1952	17	12.6
1953	17.4	12.7
1954	13	12.1
Minimum	4	4
Maximum	45	25

2. Dose of Radioiodine

Table 4 presents figures on the average initial dose of I^{131} in millicuries given each year of the study. The average dose of 4 mc. used during 1948 in the treatment of exophthalmic goiter (non-nodular) was increased in successive years because of a high incidence of persistent or recurrent thyrotoxicosis after initial treatment dose. The initial dose has now become stabilized at approximately 12 mc. The average quantity of I^{131} used for the first treatment dose in

TABLE 5.—*Doses per Patient*

Doses/Patient	Patients with Nodular Goiter		Patients with Non-Nodular Goiter	
	No.	%	No.	%
1	52	64	196	79
2	24	29	45	18
3	4	5	6	2
4	2	2	0	0
5	0	0	1	<1

TABLE 6.—*Total Dose in Relation to Goiter Size*

Goiter Size	Nodular Goiter		Non-Nodular Goiter	
	Av. Dose, Mc.	Patients, No.	Av. Dose, Mc.	Patients, No.
+	16	35	15	174
++	16.6	32	17	60
+++	47	12	17	14
++++	37	3	..	0

treating nodular goiters was increased from an average of 6 mc. in 1948 to an average of 17 mc. in 1952 in an attempt to make the person well with one dose. This quantity was decreased to an average of 13 mc. in 1954 because of occurrence of untoward reactions from this relatively large dose of radioiodine, primarily in older persons with large nodular goiters and congestive heart failure. It is no longer our aim to make persons with nodular toxic goiters well by the administration of one dose of I^{131}. Table 5 presents details of how frequently more than one dose of I^{131} was given to a patient.

Fifty-eight, or 71%, of 82 patients with toxic nodular goiter and 194, or 78%, of 248 patients with non-nodular toxic goiter were judged to be thyrotoxicosis-free at the time of this review. A higher per cent of patients with nodular goiters than of patients with non-nodular goiters required multiple doses of I^{131} to make them well. No patients with nodular goiters required more than four doses. Nevertheless, these doses were given at three-month intervals and therefore such patients were not made well until about an average of one year had elapsed. The only patient with non-nodular goiter treated with more than three doses had true hyperthyroidism originally but unnecessarily was later given a fourth and fifth dose of I^{131} before we proved that she now suffered from thyrotoxicosis factitia.[8]

Table 6 represents an attempt to correlate average total dose with initial goiter size. As long as relatively large numbers of patients are involved, there is a rough correlation between increased goiter size and increased dose of I^{131}. Our figures suggest that the patient with the large nodular goiter requires a larger total dose of I^{131} to render him euthyroid than the patient with an exophthalmic goiter of comparable size. This observation has been recorded before.[9]

Table 7 presents data to demonstrate that resolution of goiter is the rule with I^{131} treatment of exophthalmic goiter but is much less common in the treatment of nodular goiter. The nodular goiter was generally larger than the exophthalmic goiter, and therefore more irradiation had to be delivered to the nodular goiter to shrink it to normal size. Futhermore, radioiodine primarily is concentrated in "hot" nodular or paranodular tissue in one or two areas of the nodular goiter,[10] while in exophthalmic goiter the radioiodine is concentrated more diffusely throughout the thyroid tissue to be irradiated. And, lastly, many nodular goiters have relatively large areas of retrogressive change that are not capable of concentrating radioiodine and therefore will not be amenable to I^{131}

TABLE 7.—*Recorded Change in Goiter Size During Treatment*

Goiter	Nodular Goiter		Non-Nodular Goiter		% of those Recorded
	Patients, No.	Follow-Ups, %	Patients, No.	Follow-Ups, %	
No change	14	24	12	6	10
Decrease	13	22	20	10	16
Gone	29	49	94	48	74

TABLE 8.—*Total Dose for Previously Thyroidectomized Patient as Compared with Nonthyroidectomized Patient*

	Total Dose of I^{131}, Mc.	
	Previously Thyroidectomized	Not Thyroidectomized
Nodular goiter	26.3	35.7
Non-nodular goiter	16.2	14.6

treatment to induce necrosis and resultant decrease in volume.

It is interesting in this regard that eight patients (2.4%) with nodular goiters had roentgenographic evidence of substernal extension of the goiter. None of these patients had roentgenographic evidence of decrease in size of substernal goiter or decrease in degree of distortion of trachea or esophagus during I^{131}-induced relief of thyrotoxicosis and frequent accompanying decrease in size of the goiter visible above the thorax. We have found no observations on this point in the literature.

Table 8 summarizes the relationship of total dose of I^{131} to the history of previous surgical thyroidectomy. It is evident that patients with toxic nodular goiter who had had a thyroidectomy previously seemed to require less radioiodine to make them well than patients with toxic nodular goiter who were not previously thyroidectomized. This is probably due to the fact that patients with toxic nodular goiter who had had a previous thyroidectomy, on the average, had smaller goiters than those not previously thyroidectomized. It was formerly thought that less radioiodine would be necessary to relieve thyrotoxicosis in a patient with exophthalmic goiter if he had persistence or recurrence of thyrotoxicosis after a previous thyoidectomy, because the goiter is usually smaller and the I^{131} uptake greater than in the nonthyroidectomized patient with exophthalmic goiter. We believe that our thyroidectomized exophthalmic goiter patients actually require more radioiodine (Table 8), because the radioiodine is released from the thyroid gland into the blood stream in thyroid hormone more rapidly by the thyroids of such patients and, consequently, less irradiation is delivered to the gland. Recent evidence has confirmed this impression.[5]

Patients with exophthalmic goiter and a history of previous surgical thyroidectomy occasionally had localized areas of nodular functional hyperplasia. These areas were detected on physical examination by the presence of one or more firm to hard nodules near the thyroidectomy scar. The diagnosis of functional hyperplasia rather than carcinoma was made by the finding of an abnormally high uptake of I^{131} on Geiger-Muller or scintillation counting and the total disappearance of the "hot" nodule three months after the administration of a relatively small dose of I^{131}. Thyroid carcinoma does not concentrate more I^{131} than normal thyroid tissue [11] and consequently does not undergo necrosis as a result of irradiation from a patient dose of only 10 mc. of I^{131}.

3. Undertreatment vs. Overtreatment

When an attempt is made to make the thyrotoxic patient well with one dose of I^{131}, the incidence of persistent or recurent thyrotoxicosis from undertreatment must be balanced against the incidence of temporary to permanent hypothyroidism from overtreatment. An average of 36% of patients with toxic nodular goiter and 20% of patients with non-nodular goiter had persistent or recurrent hyperthyroidism after one dose of radioiodine. Table 9 shows that we induced temporary or permanent hypothyroidism in the same per cent (20%) of patients with exophthalmic goiter but in only 10% of patients with toxic nodular goiter. No attempt was made to analyze the incidence of temporary as compared with permanent hypothyroidism. We originally attempted the one-dose method of treating thyrotoxicosis because our patients were referred from distant places. Also, one advantage of radioiodine therapy is that the patient can be made well in three months, in contrast to a more indefinite period of time required for relief of thyrotoxicosis with antithyroid drugs. Furthermore, when patients are treated with

Table 9.—*Unpleasant Effects from* I^{131}

	Nodular Goiters			Non-Nodular Goiters	
	Patients, No.	Follow-Ups, %		Patients, No.	Follow-Ups, %
Thyroiditis	3	5		7	4
Worsening of thyrotoxicosis	2	3	10	4	2
Crisis	4	7		0	..
Hypothyroidism	6	10		39	20
Over-all incidence of hypothyroidism		15%			

repeated small doses of I^{131}, the last dose, even though small, may still result in the appearance of permanent hypothyroidism. The high incidence of hypothyroidism experienced in our patients using the one-dose method suggests, however, that it would be informative to treat a similar series of patients with fractionated doses so that the relative advantages and disadvantages of the two methods may be compared.

4. Unpleasant Effects from Radioiodine

Table 9 also presents figures on the incidence of other unpleasant clinical states encountered after the administration of radioiodine in the treatment of hyperthyroidism.

Thyroiditis.—Only 4% to 5% of patients complained of symptoms of irradiation thyroiditis, even though we attempted to treat our patients with one relatively large dose of I^{131}. Symptoms referable to thyroiditis were usually so mild that they were elicited only on careful questioning. They tended to occur in patients with nodular goiter given larger than average amounts of I^{131} and patients with exophthalmic goiter with a bruit audible over the thyroid gland.

Thyrotoxicosis Made Worse.—Exacerbation of the thyotoxic state, presumably because we withheld antithyroid drugs and because the thyroid gland dumped stored thyroid hormone into the circulation as a result of radioiodine-induced thyroiditis, most commonly occurred in old persons with toxic nodular goiter in association with generalized arteriosclerosis, especially when there was significant evidence of cerebral and coronary artery sclerosis. Three elderly patients with a history indicative of cerebral arteriosclerosis developed a temporary cerebral arteriosclerotic psychosis. Table 9 shows that 10% of patients with toxic nodular goiter were made temporarily worse, as contrasted with 2% of patients with exophthalmic goiter. We now attempt to avoid this complication by giving repeated small doses of I^{131} to poor risk patients and pretreating them with bed rest and antithyroid medication when the thyrotoxicosis is severe.

Thyroid Crisis or Death.—Thyroid crisis may result from I^{131} therapy for the same reasons that thyrotoxicosis may be made worse. Death from thyroid crisis has been reported.† There is no evidence that any of our patients died of thyroid crisis. Two patients with nodular toxic goiters and two patients with non-nodular toxic goiters died within the first three months after I^{131} therapy. The two deaths in patients with exophthalmic goiter were from myasthenia gravis of 37 years' duration in a woman 48 years old, 3 months after a treatment dose of 10 mc. and after complete relief of thyrotoxicosis (autopsy), and from mesenteric vascular thrombosis in a 35-year-old woman 1 month after 13 mc. of radioiodine (autopsy). The two deaths in patients with toxic nodular goiter within 3 months of I^{131} therapy were from post-thoracentesis shock, with death 15 minutes after the aspiration of 900 cc. of pleural fluid and 13 days after the administration of 10 mc. of I^{131} (autopsy), and bacteremia from Micrococcus pyogenes var. aureus (Staphylococcus aureus) 10 days after supracondylar amputation of the right leg for diabetic gangrene and 18 days after the administration of 15 mc. of I^{131} (autopsy).

5. Thyroidectomies After I^{131} Relief of Hyperthyroidism

Seven patients with nodular toxic goiter are known to have had surgical thyroidectomies performed after I^{131} treatment of thyrotoxicosis. The thyroidectomy was performed in each instance because of persistent goiter. The pathologist reported adenomatous goiter with moderate to marked retrogressive change in each instance, but no evidence of carcinoma or Hashimoto's thyroiditis. One patient with non-nodular toxic goiter had a surgical thyroidectomy performed to remove residual goiter. The pathologist reported the presence of colloid goiter and no carcinoma or Hashimoto's thyroiditis.

No significant correlation was observed between the dosage of radioiodine and morph-

† References 12 and 13.

ology of the surgical or autopsy specimen of thyroid gland. The 10 patients with toxic nodular goiter upon whom autopsy (three) or thyroidectomy (seven) was performed previously had received an average total dose of 35 mc. of I^{131}, the maximum total dose being 116 mc. and the minimum, 10 mc. The three patients with exophthalmic goiter upon whom an autopsy (two) or thyroidectomy (one) was performed had received doses of 10, 10, and 15 mc., respectively. The pathologist described an unusual histologic picture in the thyroid of only one of these patients. She was the patient with exophthalmic goiter who suffered from myasthenia gravis and received 10 mc. of I^{131} three months prior to death. Grossly, her thyroid measured $3.5 \times 2 \times 2$ cm. and weighed 8 gm. It was grayish-brown and firm. The cut surface displayed a markedly fibrotic parenchyma devoid of nodules or adenomata. The microscopic features were reported as follows: "Very severe chronic fibrosing thyroiditis with abundant dense and diffuse scar tissue, interspersed with areas of lymphoid hyperplasia. Focal areas of marked and atypical hyperplasia of acinar epithelium. Sclerosis of vessels with some dilatation of vascular channels." †

The lack of Hashimoto's thyroiditis in these 13 patients with hyperthyroidism and treated with I^{131} is in contrast to the findings of Lindsay and co-workers.[14] They observed the presence of Hashimoto's thyroiditis in 9 of 23 glands and regarded this lesion as one effect of internal radiation of the hyperplastic thyroid gland. In a later study [4] they found multiple benign neoplastic nodules in three of the irradiated hyperplastic glands. It was their opinion that these neoplasms appeared to have originated from intrafollicular epithelial proliferation of the Hashimoto thyroiditis. Two glands, one irradiated with I^{131} and one irradiated with external x-rays, were found to have multiple adenomas 6 and 21 years, respectively, after the first irradiation. It is their opinion that these observations suggest that thyroid carcinomas may eventually develop in human hyperplastic thyroid glands after long periods following irradiation.

† Dr. C. V. Weller, Chairman, Department of Pathology.

6. Heart Disease

Heart disease was recorded to be present in 41 patients, or 50%, of those treated for toxic nodular goiter. Forty-four patients, or 18%, with exophthalmic goiter were said to have heart disease. Eighteen patients, or 22%, with toxic nodular goiter were noted to have auricular fibrillation. Twenty-one patients, or 8%, with exophthalmic goiter were recorded as having this cardiac arrhythmia. It is interesting to observe that only 39% of the patients with toxic nodular goiter and auricular fibrillation were noted to convert to regular rhythm, while 81% of patients with non-nodular goiter and auricular fibrillation converted to normal sinus rhythm at the time of disappearance of thyrotoxicosis. The aforementioned figures on the incidence of heart disease in our hyperthyroid patients include more than heart disease complicated by congestive heart failure. It is interesting, however, to note that Andrus recorded that 33% of patients with toxic nodular goiter and 15% of patients with exophthalmic goiter have coexisting congestive heart failure.[15] Our figure of 81% for the incidence of conversion of auricular fibrillation to normal rhythm after I^{131} therapy is comparable to the figure of 71.5% conversion after surgical thyroidectomy for toxic goiter.[16] The fact that 61% of the patients with toxic nodular goiter in our series failed to convert to normal sinus rhythm after I^{131} relief of thyrotoxicosis is attributable, in our opinion, to the presence of an increased incidence of hypertensive and arteriosclerotic heart disease in these older patients (see Table 1). Even in 1928, when people died earlier in life from other causes, Hurxthal [17] found that 50% of all thyrocardiacs suffered from arteriosclerotic or hypertensive heart disease. It is probable that the great majority of patients with auricular fibrillation who had had their hyperthyroidism adequately treated with I^{131} and failed to convert to regular

rhythm had underlying nonthyrogenic heart disease sufficient to cause persistence of this arrythmia.

7. Exophthalmos

Table 10 presents average Hertel exophthalometer measurements in millimeters for both eyes in the left-hand column. Numbers in the remaining six columns designate the number of patients with Hertel exophthalmometer measurements ranging from 10 to 26 mm. The bold-face figures are at the level of the median exophthalmometer measurements made at the time of administration of the treatment dose of radioiodine, three months later, and six months later. It is evident that the median exophthalmometer measurement in each group of patients with toxic goiter was higher than in persons without thyroid disease and that the eyes of patients with exophthalmic goiter were more prominent than the eyes of patients with toxic nodular goiter. No significant increase in the median of exophthalmometer measurements is seen after radioiodine treatment in either group of patients. It is noteworthy, however, that about one-third of the patients in each goiter category were recorded as showing an increase in exophthalmometer measurements and about an equal number were recorded as showing a decrease in exophthalmometer measurements. It is also important to point out that our patients included more than the usual number of patients with malignant or progressive exophthalmos, because we have been particularly interested in seeing these patients and have used radioiodine as the treatment of choice for thyrotoxicosis when it is accompanied by progressive exophthalmos. Thirteen per cent of our patients with exophthalmic goiter and six per cent of patients with toxic nodular goiter were recorded to have malignant or progressive exophthalmos. More work is needed in the compilation of accurate exophthalmometer measurements on patients to be treated for hyperthyroidism with I^{131} to prove our observation that only about one-third of such patients will show progression of exophthalmos and that about one-third will show a decrease in measurements. If these figures are confirmed, however, it will appear that, when a patient has thyrotoxicosis and true exophthalmos, I^{131} treatment for the hyperthyroidism might result in a lower incidence of exophthalmos than thyroidectomy, since Dobyns and Haines found that two-thirds of 233 surgically thyroidectomized patients showed an increase in exophthalmos of more than 1 mm.[6]

Table 10.—*Exophthalmometer Measurements at Time of First Dose and Three Months and Six Months Later*

Measurements, Mm.	Patients with Nodular Goiters, No.			Patients with Non-Nodular Goiters, No.		
	At Time of Dose	After 3 Mo.	After 6 Mo.	At Time of Dose	After 3 Mo.	After 6 Mo.
10	..	..	..	1	..	..
11	..	..	..	1	..	..
12	2	..	..	..	..	..
13	2	1	..	2	..	..
14	..	1	..	5	1	..
15	1	1	1	9	5	..
16	1	..	..	7	4	1
17	2	4	1	7	6	3
18	**6**	**4**	**3**	16	14	5
19	2	2	1	15	6	4
20	..	..	..	**19**	**13**	4
21	2	1	..	10	9	**3**
22	2	2	..	10	8	4
23	1	1	..	14	7	5
24	..	..	1	7	3	**3**
25	2	..	..	2	2	3
26	1	1	..	4	6	3

Conclusions and Summary

Three hundred thirty patients were given one or more treatment doses of radioactive iodine (I^{131}) from Feb. 24, 1948, to Jan. 1, 1955. An attempt was made to "cure" the thyrotoxicosis with one dose of I^{131}. The majority of the 82 patients with nodular toxic goiter were treated with I^{131} because subtotal thyroidectomy was refused by the surgeon or by the patient or because preoperative preparation with antithyroid drugs took longer than four months. The majority of patients with exophthalmic goiter were treated with I^{131} because they had had a previous thyroidectomy and now suffered from persistence or recurrence of their thyrotoxicosis or because this was the treatment of choice for small exophthalmic goiters in persons over 40 years of age. In this selected group of patients 4% to 5% of patients had ex-

hibited intolerance to strong iodine solution U. S. P. (Lugol's solution) and antithyroid drugs. Six per cent of patients with toxic nodular goiter and thirteen per cent of patients with exophtalmic goiter had progressive exophthalmos before treatment of their thyrotoxicosis with I^{131}. Thirty-four per cent of patients with toxic nodular goiter and fourteen per cent of those with exophthalmic goiter were judged to have inadequate preoperative preparation after four months of treatment with iodine and antithyroid drugs. The average initial dose of I^{131} used in treating exophthalmic goiter has increased from the 4 mc., used in 1948, to about 12 mc. because of an incidence of persistent and recurrent thyrotoxicosis of 20% after one dose of I^{131}. The initial dose of I^{131} used in treating nodular goiter patients was increased from 6 mc., in 1948, to 17 mc., in 1952, but has since been decreased to 13 mc. because of a 10% incidence of worsening of thyrotoxicosis and/or induction of thyroid crisis, allowed by withholding antithyroid medication after I^{131} therapy or induced by I^{131} irradiation thyroditis effecting sudden dumping of large amounts of stored thyroid hormone into the circulation. The 10% incidence of hyperthyroidism in toxic nodular goiter and the 20% incidence of temporary and permanent hypothyroidism in exophthalmic goiter after the one-dose method of treatment suggests that a controlled similar series of patients should be treated with fractionated doses in an attempt to decrease the incidence of I^{131}-induced hypothyroidism. Patients with nodular goiters appeared to require a larger dose of I^{131} to become euthyroid than patients with exophthalmic goiter of comparable size. Resolution of goiter is the rule with I^{131} treatment of exophthalmic goiter but is much less common in the treatment of toxic nodular goiters. No substernal goiter was observed to produce less distortion of the trachea or shrink in size, as observed by roentgenograms, during the relief of thyrotoxicosis with I^{131}, even when the coexistant visible goiter in the neck decreased in volume by as much as 60%. Contrary to our early expectations, patients with exophthalmic goiter persistent or recurrent after a previous thyroidectomy require a larger average total dose for relief of thyrotoxicosis than patients with exophthalmic goiter not previously treated by surgical thyroidectomy. Patients with persistent or recurrent toxic nodular goiter, on the other hand, required a smaller dosage of I^{131} than those with toxic nodular goiter who were not previously thyroidectomized. Five per cent of patients developed minor symptoms of irradiation-induced thyroiditis. Usually these patients had large nodular goiters or moderately severe exophthalmic goiter with a bruit audible over the gland. No patient died from thyroid crisis. Seven patients with toxic nodular goiter and one patient with exophthalmic goiter required subsequent surgical thyroidectomy because of goiter persistent after relief of thyrotoxicosis. Out of these surgical thyroid specimens and five thyroids examined at autopsy after I^{131} treatment, only one thyroid gland showed effects that resembled morphological changes described by others as due to I^{131}. No carcinoma was found. Fifty per cent of patients with toxic nodular goiter and eighteen per cent of patients with exophthalmic goiter were recorded to have coexistent heart disease. Twenty-two and eight per cent, respectively, were observed to have auricular fibrillation. Thirty-nine per cent of patients with toxic nodular goiter and auricular fibrillation and eighty-one per cent of patients with exophthalmic goiter and auricular fibrillation converted to normal sinus rhythm when relieved of their thyrotoxicosis with I^{131} therapy. The median exophthalmometer measurements of toxic nodular and exophthalmic goiter patients showed no significant change during six months after I^{131} therapy for relief of coexistent thyrotoxicosis. About one-third of the patients showed an increase and one-third showed a decrease in exophthalmometer measurements during this same period.

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Nucleophagocytosis

Studies on Three Hundred Thirty-Six Patients

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The L. E. cell phenomenon has been considered to be highly specific for systemic lupus erythematosus.* Nevertheless, it has been reported in isolated cases of other diseases † and has been repeatedly demonstrated in association with severe hypersensitivity reactions to penicillin,‡ tetanus antitoxin, hydantoin,[10] and hydralazine.§

The resulting hypothesis that the L. E. cell might represent an immunologic phenomenon led to the attempt to reproduce it by incubating leucocytes with antileucocytic rabbit serum.‖ The cells thus produced resembled, but were not identical with, the L. E. cell. The inclusion body was still recognizable as a secondary nucleus with preserved chromatin pattern, in contrast to the "smoky" homogenized L. E. inclusion body. Patients with hypersensitivity states frequently may show such nucleophagocytosis [17] and occasionally the L. E. cell phenomenon.¶ Zimmer and Hargraves [18] noted that positive L. E. preparations in patients with systemic lupus erythematosus showed increased numbers of nucleophagocytes as well as true L. E. cells. Such nucleophagocytes could also be seen in the absence of L. E. cells. These observations led to the present study of the significance of nucleophagocytosis. The incidence was determined in normals and in patients with various diseases, including hypersensitivity reactions. The occurrence of this phenomenon in patients receiving penicillin without the development of hypersensitivity was also studied to determine the possible effect of this agent in the development of nucleophagocytosis.

TABLE 1.—*Groups of Patients Studied for Nucleophagocytosis*

		Patients, No.
Group I.....	Normals	20
Group II.....	Patients studied prior to treatment with penicillin	98*
Group III.....	Patients studied after treatment	86*
Group IV.....	Patients with clinical manifestation of drug hypersensitivity	43
Group V.....	Diagnostic group	126

* Thirty-seven patients were studied both before and after penicillin therapy.

METHODS AND TERMINOLOGY

The patients studied are listed in Table 1. The patients of Groups II and III had no evidence of drug hypersensitivity, while those patients who had allergic reactions to penicillin are included in Group IV. The "diagnostic" group (Group V) included a number of patients with symptoms consistent with the diagnosis of one of the collagen diseases. Within this group there also were several patients who received hydralazine for varying periods without developing fever, arthralgia, or other manifestations of the rheumatoid state. Those patients who did develop such reactions were considered with Group IV.

The method of Zimmer and Hargraves [18] was used in the preparation of the specimens of serum to be tested for the presence of the L. E. cell phenomenon and nucleophagocytosis. These authors have observed that this method not only allows

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* References 1-4.
† References 4-7.
‡ References 8-10.
§ References 11 and 12.
‖ References 13-16.
¶ References 8-10.

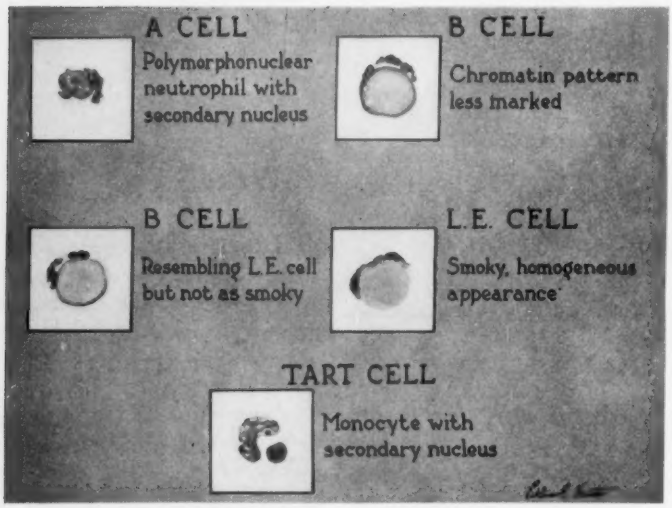
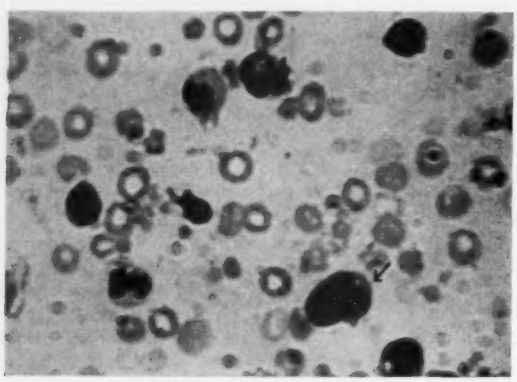


Fig. 1.—Diagrammatic representation of the types of nucleophagocytes and the L. E. cell. Note the loss of chromatin pattern shown by the two types of B-cell, as compared with the A-cell, and the resemblance of the B-cell to the L. E. cell.

the demonstration of the L. E. cells but also accentuates nucleophagocytosis.

In accordance with the nomenclature suggested by Hargraves,[1] the "tart" cell refers to the phagocytizing monocyte with the nuclear inclusion body. When the engulfing cell is a polymorphonuclear leucocyte it may resemble the true L. E. cell, if sufficient homogenization of the chromatin pattern of the secondary nucleus has occurred. (The terms inclusion body, engulfed nucleus, and secondary nucleus are used synonymously.) Because of the varying degree of homogenization of the secondary nucleus, these cells ("nucleophagocytes") have been arbitrarily classified as Type A and Type B (Figs. 1 to 3). The A-cell represents the polymorphonuclear leucocyte in which the engulfed nucleus shows a well-preserved chromatin pattern. The primary nucleus is pushed toward the periphery. In the B-cell the secondary nucleus is more pyknotic and shows varying degrees of homogeneity. The primary nucleus usually is more flattened than in the A-cell and may be as crescentric as in the L. E. cell. The engulfed nucleus does not have

Fig. 2.—A-cell and "tart" cell (arrow).



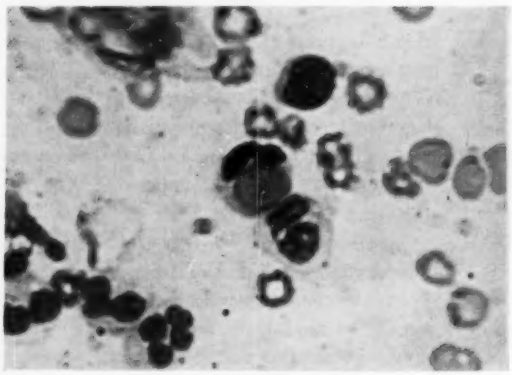


Fig. 3.—B-cell.

the smoky appearance of the inclusion body of the L. E. cell, and it has a characteristic basophilic rim. Nucleophagocytosis is not associated with rosette formation, another feature helpful in distinguishing it from the L. E. cell phenomenon. In the presence of B-cells, tart cells and A-cells usually can be seen.

RESULTS

The incidence of nucleophagocytosis in 20 normal subjects is shown in Table 2. It is apparent that by this method the blood of normal persons consistently shows nucleophagocytosis of the A and tart cell type. In only 1 of 20 normal subjects, however, were B-cells seen. It is of interest that this otherwise normal person has a mild eosinophilia and is subject to hay fever, although he did not have attacks during the period of study.

TABLE 2.—*Incidence of Nucleophagocytes in Twenty Normal Subjects*

Type of Nucleophagocytosis	Subjects, No.
Tart cells and A-cells	19
Tart, A-cells and B-cells	1

In only 5 of 98 patients with various diseases studied before the use of penicillin were B-cells found (Table 3). The effect of the administration of penicillin to patients with various infections is shown in Tables 4 and 5. B-cells occurred in 15% of the patients who had received penicillin for varying periods (14 to 22 days) (Table 4). This appears significantly greater than the 5% incidence

TABLE 3.—*Incidence of B-Cells in Patients Prior to Use of Penicillin*

Diagnosis	Patients, No.	Patients with B-Cells, No.
Pneumonia	26	1
Chronic respiratory infections	14	1
Streptococcal sore throat	4	1
Rheumatic fever	4	1
Erysipelas	2	0
Miscellaneous *	48	1
Total	98	5

* This group consists of patients with various diseases, e. g., diabetes, tuberculosis, cirrhosis, glomerulonephritis, carcinoma, etc., to whom penicillin was given because of superimposed infections. The one patient with B-cells had a metastatic carcinoma of the prostate, treated with adrenalectomy.

TABLE 4.—*Incidence of B-Cells in Patients After Use of Penicillin*

Diagnosis	Patients, No.	Patients with B-Cells, No.
Pneumonia	30	9
Chronic respiratory infections	20	3
Streptococcal sore throat	4	0
Rheumatic fever	4	1
Miscellaneous	27	0
Total	85	13

TABLE 5.—*Incidence of B-Cells Before and After Penicillin Therapy*

Diagnosis	Patients, No.	Patients with B-Cells	
		Before Therapy	After Therapy
Pneumonia	13	1	5
Streptococcal sore throat	2	1	0
Chronic respiratory infections	2	1	2
Rheumatic fever	2	1	0
Miscellaneous	9	0	0
Total	36	4	7

TABLE 6.—*Incidence of B-Cells and L. E. Cells in Hypersensitivity Reaction*

Patients, No.	Agent	Patients with B-Cells	Patients with L. E. Cells *
26	Penicillin	9	1
4	Tetanus antitoxin	2	..
2	Hydralazine †	1	1
1	Quinine	1	..
1	Unknown, probably food	1	..
9	Miscellaneous	..	..
		14	2

* "Tart," A-, and B-cells were also present.

† Seven other patients who had received hydralazine for two to four months and had tolerated it well did not develop L. E. or B-cells during the time of observation.

($P<0.05$) in a similar group of patients who had not received penicillin. These results, however, are not supported by the analysis of 37 patients who were tested both before and after the administration of penicillin (Table 5). The incidence of B-cells in these patients was not appreciably different before and after treatment. It is of interest that in four patients such cells, which had been present initially, disappeared after treatment, while they were noted after treatment only in six others. A much higher incidence of B-cells was noted in patients with evident drug hypersensitivity (Table 6). Of 43 patients with allergic reaction to the agents listed in Table 6, 14 had B-cells. In two patients L. E. cells and rosettes were demonstrated. These two patients had severe reactions to penicillin and to hydralazine, respectively, but in the entire group a relationship between the occurrence of B-cells and the severity of the allergic reaction was not apparent.

During the period of this study the L. E. test was performed in 126 patients for diagnostic reasons (Table 7). In three patients L. E. cells were demonstrated. In two the clinical picture was consistent with a diagnosis of systemic lupus erythematosus. In a third patient, reported elsewhere,[19] a diagnosis of postnecrotic cirrhosis was established (Table 7, Case 9). Nucleophagocytes of the B type were also seen in these three patients. In 13 patients with similar syndromes these cells were seen without L. E. cells.

Erythrophagocytosis was seen in almost all preparations studied and seemed to be at least as common as nucleophagocytosis of the A- and "tart" cell type. In preparations showing B-cells erythrophagocytosis was prominent. No further evaluation of this phenomenon was attempted in this study.

COMMENT

Under the condition of this study several types of nucleophagocytes were seen, depending on the identity of the phagocytizing cell (monocyte or polymorphonuclear leucocyte) and the degree of homogenization of the engulfed nucleus. In the case of the phagocytizing monocyte ("tart" cell), the chromatin pattern of the inclusion body was usually visible. In the analysis of the phagocytizing polymorphonuclear leucocytes, however, it seemed appropriate to categorize the cells according to the degree of homogenization of the secondary nucleus. The arbitrary distinction between A- and B-cells disclosed certain differences in their incidence among the 336 patients studied (Tables 3 and 4). The "tart" and A-cells were seen too frequently in the normal person and in many patients to acquire clinical significance. The B-cells, however, were seen only rarely in normal persons but frequently in patients with hypersensitivity reactions and certain diseases with a postulated immunologic basis. The administration of pencillin did not result in a significantly higher incidence of such

TABLE 7.—*Incidence of the L. E.-Cell Phenomenon and Nucleophagocytosis in 126 Patients Tested for Diagnostic Reasons (Only the Positives are Included)*

Final Diagnosis	B-Cells	L. E. Cells *
1. Lupus erythematosus	..	2
2. Rheumatoid arthritis	4	..
3. Periarteritis nodosa	1	..
4. Nephrotic syndrome	2	..
5. Fever of unknown origin	1	..
6. Cardiomegaly of unknown cause	1	..
7. Glomerulonephritis	2	..
8. Pneumonitis	1	..
9. Eosinophilia due to parasitic infestation	1	1
	13	3

* "Tart," A-, and B-cells were also present.

cells unless it was associated with an allergic reaction.

These observations are in agreement with those of other workers who have reported nucleophagocytosis # in patients with hypersensitivity reactions. The similarity of the nucleophagocyte with an homogenized secondary nucleus to the L. E. cell has been emphasized by Meyler,[17] Leoni,[7] and Miescher.* The cells have even been called "pseudo-L. E. cells."[19]

Nucleophagocytosis has been produced experimentally under the influence of antileucocytic antibodies.† Incubation of leucocytes with rabbit antileucocytic serum results in cells similar in appearance to the L. E. cell. Although these were described as identical with the L. E. cell,[16] on morphologic analysis, they seemed to be nucleophagocytes similar to the A- and B-cells of the present study. True L. E. cells have also been demonstrated in patients with hypersensitivity.‡ The morphologic similarity between those two cells and their apparent relationship to immunological processes suggests that they might be related to each other. The occurrence of both in patients with systemic lupus erythematosus also bespeaks the possibility of such a relationship. It is generally accepted that the primary process in the morphogenesis of the L. E. cell is nucleolysis followed by the phagocytosis of the lysed nucleus, leading to the formation of an L. E. cell (Fig. 4). The intriguing similarity of the L. E. cell to the pseudo-L. E. cell of Miescher (B-cell in this study) and the simultaneous occurrence of nucleophagocytes and L. E. cells raises the possibility of an alternative mode of formation of the L. E. cell. This may consist of initial nucleophagocytosis with subsequent lysis of the nucleus. In this respect it is of interest that a nucleolytic system considered partly responsible for the formation of the L. E. cell has been found within the leucocyte.[21]

Nucleophagocytosis seems to be a phenomenon of clinical and theoretical significance. Occurring widely in normal persons and in disease, it assumes clinical significance directly proportional to the degree of homogenization of the secondary nucleus. The relationship of this phenomenon to lupus erythematosus and the L. E. cell and of the latter to hypersensitivity requires further study.

The occurrence of L. E. cells in patients with drug hypersensitivity seems to challenge the specificity of the L. E. cell phenomenon. The interpretation, however, that this represents a "false positive test" is an oversimplification, as the role of hypersensitivity in the genesis of lupus erythematosus has been emphasized repeatedly.§

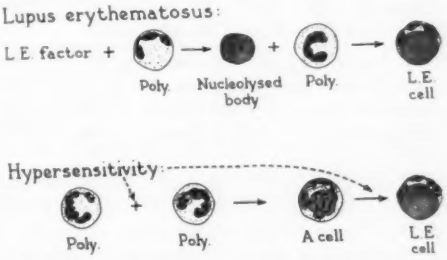


Fig. 4.—Postulated alternative modes of genesis of the L. E. cell.

The transient presence of the L. E. cell phenomenon in patients with drug hypersensitivity paralleling the self-limited clinical disease contrasts with the persistence of the L. E. cells and prolonged duration of clinical disease in patients with untreated classical lupus erythematosus. Perhaps the "false positive L. E. tests" in patients with drug hypersensitivity should be considered to indicate the presence of acute acquired reversible lupus erythematosus with a clear etiology and a good prognosis, in contrast to acute idiopathic systemic lupus erythematosus, an irreversible disease with a gloomy prognosis.

SUMMARY AND CONCLUSIONS

In a study of nucleophagocytosis in the blood of 336 patients, several types of nucleo-

References 10 and 17.

* References 10 and 20.

† References 13-16.

‡ References 8-10.

§ References 21 and 22.

phagocytes have been seen. Tart cells and polymorphonuclear nucleophagocytes with no homogenization of the secondary nucleus were seen in normal persons and in patients with miscellaneous diseases. Polymorphonuclear nucleophagocytes with homogenized secondary nuclei were seen in hypersensitivity states and rarely in normal persons. The significance of these observations is discussed.

ADDENDUM

After the completion of this study Weiss [24] described similar observations on nucleophagocytosis in hypersensitivity reactions.

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The Ileocecal Valve and Papilla

Observations Relating to Pathophysiology of Acute Colon Obstruction

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In 1904 Sir William Macewen,[1] Regius Professor of Surgery at the University of Glasgow, in his lecture on the cecum aptly stated that just as the informed citizen learns world geography by perusing the news of foreign wars so the clinician becomes involved in anatomic studies by skirmishes with clinical problems. Thus, anatomical consideration is given the so-called ileocecal valve because of interest in problems of acute large bowel obstruction. This structure supposedly prevents regurgitation of colonic material and gas into the ileum and so accounts for the status of "closed loop" in obstructive lesions of the colon.[2] Allegedly, 10% of these valves are incompetent, because the inferior leaflet is absent. In such cases, the obstructed colon supposedly decompresses itself into the small intestine.

In our experience a much larger percentage of acute colon obstructions exhibit signs of associated small bowel obstruction, and scout films of the abdomen often show loops of small bowel distended with gas and fluid levels.[3] Table 1 summarizes data of an incidence of more than 20% of moderate to marked gas in the small intestine. Also,

TABLE 1.—*X-Ray Evidence of Associated Small Intestine Obstruction in Cases of Acute Colon Obstruction Due to Carcinoma, 153 Patients*

	Colon Obstruction			
	Partial (69) *		Complete (84) *	
	No.	%	No.	%
Film taken	22	...	60	...
Small intestine distention				
Slight	4	5.8	7	8.4
Moderate	2	2.9	12	14.3
Marked	2	2.9	15	17.9
Total small intestine distention	8	11.6	34	40.6

* Number of cases is given in parentheses.

at the operating table when we make colostomies for tightly distended colons in patients with acute large bowel obstruction due to cancer, in many instances, the small bowel also shows distention. If this distention is due to an incompetent ileocecal valve, why is the colon not decompressed? Furthermore, we have evidence that the obstructed colon in the experimental animal contains material that does not largely arise from putrefaction and secretion. The gas and fluid that accumulate and the increments of such that raise the intraluminal pressure above the critical portal pressure come largely from ileal emptying into the cecum. It is doubtful that the obstructed colon generates gas and material under pressure to the extent of forcing the ileocecal valve. Experimentally, the total colon closed at both ends, with ileal emptying diverted into the rectum, will survive indefinitely[4] without marked distention or circulatory embarrassment.

The questions that concerned us at the outset were the following:

1. How many ileocecal valves have an absent leaflet and are incompetent?

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2. Does the anatomy of the ileocecal junction justify the valve concept?
3. How does the ileocecal junction in man appear and operate in vivo?
4. Is competency of clinical significance?
5. What is the mechanism at the ileocecal junction that would explain the relatively large number of cases of associated small bowel distention in acute large bowel obstruction?

The "valvula coli" has been described in anatomical texts as two crescentic segments, the valvulae (or lips), the ends of which are prolonged and extend around the cecal wall as lateral and medial folds, the frenula. The lateral and medial limits of the ileocolic orifice, where the valvulae meet, have been called commissures. To be accurate, according to DiDio,[5] we should speak of the ileocecocolic orifice, since in all recorded cases (Fig. 1) it is located at the junction of cecum and ascending colon in the posteromedial aspect. Some writers[6] have called the part of the frenulum that meets the commissure, the arch.

The anatomy texts of Spalteholtz[7] and Sabotta and McMurrich[8] both state that the cecum is below the "valvula coli." They both stress the frenular structure which suspends the valve and demarcates cecum from ascending colon. Friedell and Wakefield[9] also indicate the importance of the frenula and state that the full development of these structures depends upon a fully developed adult cecum. In the textbooks by Deaver,[10] Callander,[11] Morris,[12] Cunningham,[13] and Gray[14] the ileocecal valve is depicted as the so-called classical "Type I" of Buirge. Apparently, anatomists have been concerned for many years about the valvelike appearance of the ileocecal junction and have speculated as to its competency. In this respect, Rutherford* in his monograph cites Meckel, Symington, Charpy, and Poirier. He notes that from the time of Fabricius d'Aquapendente, in the Seventeenth Century, through Riolan to Cruveilhier and other illustrious anatomists, pathologists, and doctors, there has been disagreement about the competency and function of the valve. It was Rutherford who pointed out that his own studies of the preserved ileocecal valve did not agree with the one case he had observed in vivo. To him is ascribed the analogy of the valve to a horse's anus (although the valve is not so explosive in its function and certainly is more graceful in its motions). Brash[13] in 1951 pointed out that many of the different descriptions of the valve are due not only to variables of development and postmortem change but also to differences in preparation and preservation of the specimens.

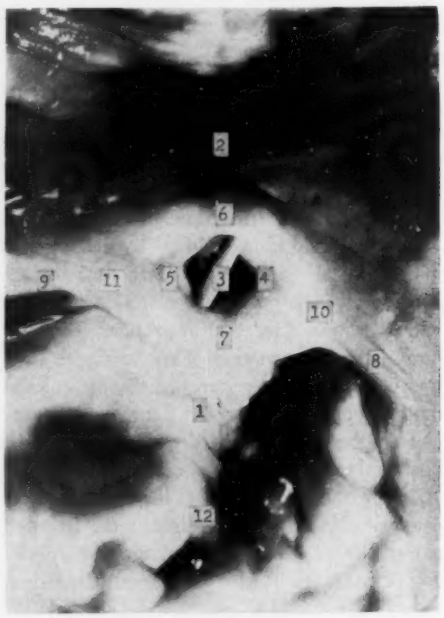

Fig. 1.—Typical ileocecal orifice, seven hours after death. Unusual is the presence of valve leaflet at lateral commissure. (*1*) Cecum, (*2*) ascending colon, (*3*) ileocecal orifice, (*4*) medial commissure, (*5*) lateral commissure, (*6*) superior valvula, (*7*) inferior valvula, (*8*) medial frenulum, (*9*) lateral frenulum, (*10*) medial arch, (*11*) lateral arch, (*12*) appendiceal orifice. (Reproduced with permission from Ulin and Deutsch,[30] *Gastroenterology*, Baltimore, Williams & Wilkins Company.)

In 1943 Buirge[6] reported gross observations on 500 ileocecal segments. These were removed from fresh cadavers, cleaned with water, filled with 10% formalin, and then suspended in vats containing 10% formalin. Consequently, the results were all on dis-

* References 15 and 16.

tended specimens fixed in formalin. His observations and measurements revealed marked variation in size and appearance of the valvular aperture (ranging from 0.3 to 3.5 cm.).

Superior lip: 0.3 to 2.5 cm. thick
0.4 to 2.5 cm. projection into cecum
Inferior lip: 0.3 to 0.6 cm. thick
0.6 cm. average projection into cecum

Of the 500 specimens there was no inferior lip in only three cases. However, it is emphasized that in 411 valves the inferior lip, in comparison with the superior lip, was incompletely developed in 75%. These measured 0.4 to 2 cm. less in length than the superior lip. In 40% of 270 classical types of complete ileocecal valves (so-called Type I), the superior lip projected more than the inferior lip. There were such marked variations in the development of the frenula that Buirge classified the valves according to the completeness of the lateral and medial arches of the frenula (Table 2).

TABLE 2.—*Classification of 500 Ileocecal Valves* *

Type I	54% fully developed valves and complete arches
Type II	13% absence of inferior arch, either mesial or lateral
Type III	6% bilateral absence of inferior arches
Type IV	24% absence of lateral or mesial frenulum (22% mesial and 2% lateral)
Type V	2% absence of both mesial and lateral frenula

* From Buirge,[6] Anatomical Record, Philadelphia, Wistar Institute of Anatomy and Biology.

In 1950 Fleischner and Bernstein [17] reported roentgen and anatomic studies of the normal ileocecal valve in man. They examined 50 specimens filled and preserved in 10% formalin as well as 200 spot films of the ileocecal area in the barium examination of patients. They noted the valve as a papillary eminence, with an operating orifice of 2 to 3 mm. in diameter. They, like DiDio,[5] stressed the oblique and tangential entrance of the ileum into the cecum and described the fused wall of terminal ileum and mesial cecum. Independently since 1948, in our dissections we have noted this cecal part of the terminal ileum and have designated the part sheathed by cecal serosa the tangential measurement. DiDio's nomenclature of "cecal ileum" should be acceptable.

Puente Dominguez † in his embryologic and anatomical studies of the ileocecal sphincter area pointed out that its development is into a muscular mammillary body around which the valve structure is organized. The muscular papilla consists not only of circular muscle derived from circular layers of the ileum and cecum but also of longitudinal muscle, which not only has to do with opening the valve but is associated with the muscular structure of the frenula and the terminal ileum to steady or fix the valve for its proper function.

DiDio [5] in his monograph presented the most extensive study of the morphology and musculature of the ileocecocolic segment in man. He, like Puente Dominguez, observed the ileocecal eminence directly through a proctoscope in a patient with a cecal fistula. He emphasized the importance of the sphincter mechanism in control of the transit of ileal material into the cecum as well as in preventing cecal regurgitation. In his monograph he states that he is convinced that the in vivo type of structure is papillary in form. The labial form seen in preserved and even in fresh cadavers is due to artifacts; the frenula are structures that are evident in cadavers and not in a living patient.

Investigators have emphasized the physiologic aspects of the orifice. There is adequate evidence of a sphincter-like action that may be more significant than the anatomic configuration in health and disease. Tönnis [20] and Hannes [21] both pointed out the fact that in cats and dogs the ileocecal orifice offers resistance to pressure. Tönnis described a definite sphincter action in isolated ileocecal preparations of cats, even after these had been denervated. He indicated that the terminal ileum behaves like the antrum of the stomach. Using barium, he demonstrated that it propels its contents by means of large peristaltic waves against the closed ileocecal valve. The valve would open and

† References 18 and 19.

close rhythmically and this depended on: (1) psychic contractions (effect of eating or fasting); (2) peristalsis of the ileum; (3) the filling condition of the cecum and ascending colon. Section of the nerves supplying the valve causes only temporary paralysis, thus indicating that extrinsic nerves have only a regulating function. The intrinsic rhythmic function is under control of the plexus of Auerbach. This work was confirmed by Henrichsen and Ivy.[22] These workers also confirmed Hannes in that irritation of the colon caused reflex closing of the ileocecal sphincter. They conclude that the vagus nerve contains both motor and inhibitory fibers for the ileocecal sphincter. The splanchnic nerves, containing only motor fibers, maintain the tone in the sphincter. Alvarez ‡ reported that the terminal 25 cm. of ileum constitutes a "breaking mechanism" which helps the ileocecal sphincter in controlling the passage of material into the colon and prevents reflux. The sphincter muscle is much more irritable than the cecal muscle or the musculature of the ileum. Consequently, the sphincter muscle would contract ahead of a wave of reversed peristalsis coming from the colon. Sperling[25] related that distention of the cecum up to certain limits may cause increased tone of the sphincter, and he cites the experiments of Heile indicating that with large bowel obstruction there is slower evacuation of the small intestine into the ileum.

I. OBSERVATION OF THE ILEOCECAL ORIFICE IN VIVO

Variations in the anatomy, especially defects in the valvulae and commissures, supposedly explain the instances of cecal-ileal regurgitation in large bowel obstruction. This rather attractive conclusion based on the study of fixed anatomical preparations is not altogether tenable in view of the in vivo appearance and physiological behavior of the ileocecal orifice. This structure has been observed in a living subject through a cecal fistula by Macewen[1] in 1904, Rutherford[15] in 1905, Short[26] in 1919, White and coworkers[27] in 1934, Palmieri[28] in 1938, Buirge[29] in 1944, Puente Dominguez[19] in 1946, and DiDio[5] in 1952. In 1950 we[30] studied this ileocecal papilla in vivo and became convinced of the primary importance of the sphincteric mechanism. In the living subject, the anatomy of the so-called ileocecal valve is such that the proper terminology should be ileocecal papilla and sphincter. The textbook description acceptable today depicting a valve is based on cadaver study and on photography of fixed preparations.

The ileocecal junction of a 70-year-old white man was observed and photographed through a 10 in. Montague sigmoidoscope passed through a cecostomy. The cecum was empty and clean. Air was introduced by the usual manual bulb compression method. The ileocecal papilla was visualized projecting neatly about 1 cm. into the cecum. The tightly closed puckered opening, marked only by the stellate configuration, did not conform with the customary postmortem picture. No frenula were apparent. Valvulae or valvelike lips limited by commissures were not present (Fig. 2). (However, for convenience of terminology we are designating the anterosuperior and posteroinferior parts of the circumference as valvulae.) The posterior rim or valvula, protruding only about 0.5 cm., was at times hidden by mucosal folds and, therefore, difficult to photograph; the anterior valvula protruded 1.2 cm. The papilla then turned slowly, gracefully, and anteriorly with about the speed of the ordinary slow-motion movie, enabling us to look at the orifice. The papilla measured 1.4 cm. in diameter. The orifice was stellate and closed and measured 0.5 cm., and it was located on the posterior mesial wall of the cecum. During the experiment it moved slowly through an arc of about 80 degrees in the sagittal plane, always pointing posteriorly. In the horizontal plane it moved through an arc of 20 degrees. Only once, by manipulation of the sigmoidoscope, did the papilla point squarely anteriorly to any extent.

One ampule of neostigmine (Prostigmin) methylsulfate 1 : 2000 was given intramuscu-

‡ References 23 and 24.

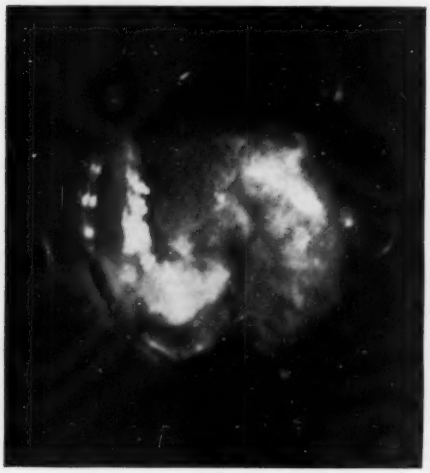

Fig. 2 (Case 1).—Ileocecal orifice in vivo. Extrusion of feculent material by ileocecal orifice. Notch at inferior angle of the ileocecal papilla is due to shadow of the sigmoidoscopic light bulb. Actually, the inferior part of the papilla was identical to the superior part shown in the photograph. (Reproduced with permission from Ulin and Deutsch,[30] *Gastroenterology,* Baltimore, Williams & Wilkins Company.)

larly. Peristalsis, which was hypoactive, became slightly more active. Atropine 1/100 grain (0.6 mg.) was given intravenously. Although the pulse increased from 80 to 105 per minute, no immediate effect on peristalsis or on the papilla was seen. After six minutes the rim, which measured about 0.45 cm. in width, flattened and narrowed to about 0.2 cm. The orifice extruded about 4 cc. of mucofeculent material. In fact, in its appearance generally, as well as its behavior in extruding material, the ileocecal papilla resembled a horse's anus.

The patient eventually died, and 30 minutes after death the sigmoidoscope was passed via cecostomy. The cecal wall was completely flaccid and collapsed. Movements of the ileocecal papilla were noted 35 to 50 minutes after death as fibrillary twitches of the valvulae, as well as movement of the entire papilla as in vivo—slow, smooth movements. In life, the papilla had more substance, more direction, and looked like a cervix protruding into the vagina. Strong air pressure could not flatten the valvulae but did produce about 1 mm. dilation of the orifice. After death, the papilla was flaccid and responded immediately and easily to slight changes in air pressure. With increase in air pressure there was visualized a shift in the direction as well as flattening and undulating motion of the valvulae. The orifice became more and more patulous, and eventually, at 55 minutes after death, the orifice

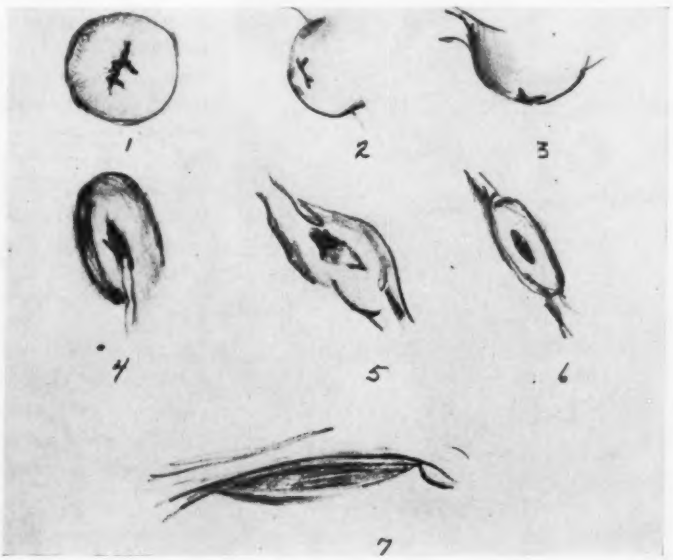

Fig. 3.—Line drawings of the observations made in the first case. (*1*), (*2*), (*3*), and (*4*) in vivo appearance of the ileocecal orifice as observed through the sigmoidoscope. In (*5*) the papilla is shown in situ, one and a half hours after death; (*6*) shows the appearance at autopsy; (*7*) is the time-honored text-book picture of ileocecal "valve." (Reproduced with permission from Ulin and Deutsch,[30] *Gastroenterology,* Baltimore, Williams & Wilkins Company.)

Fig. 4 (Case 2).—Photograph of ileocecal orifice in vivo.

was 12 mm. open. We were then able to look into the lumen of the ileum (Fig. 3). At autopsy the papilla was examined, and the following measurements were made: papilla, 2×0.8 cm.; orifice, 5×2 mm.; valvulae protruded 4 mm. We found a completely elliptical valve, as described in some anatomical texts, which took whatever shape it was placed in. Manometric study revealed that 35 cm. of water pressure was required to regurgitate from cecum to ileum.

Fig. 5 (Case 3).—Photograph of ileocecal orifice in vivo.

The second case of ileocecal valve observed by us in vivo was that of a white man, 62 years of age, and was exposed at the operating table by one of our associates, Dr. William Y. Lee § (Fig. 4). The patient was under spinal anesthesia, and the valve was motionless. The sphincter was papillary but more oval-shaped; the mucosa was a deep red.

The third instance was a white man, 68 years of age, also operated on by Dr. Lee and Dr. E. D. Sharpless. Exploration was done because of a radiologic diagnosis of tumor of the ileocecal valve. Histologic sections revealed no evidence of any pathological state and showed only normal, smooth muscle structure of the sphincter. This orifice was not observed in vivo, its exposure of course being after resection (Fig. 5). However, it was carefully palpated at the operating table and it felt firm and conical. Figure 6, an air-contrast film, shows a similar orifice.

We observed the ileocecal orifice in six dogs under light veterinary intravenous pentobarbital (Nembutal) anesthesia. Figure 7 is fairly representative of the papillary

§ Lee, W. Y., and Sharpless, E. D.: Personal communication to the authors.

structure seen. Under anesthesia, the sphincters were generally inactive but offered resistance to digital insertion.

II. ANATOMICAL MEASUREMENTS IN PRESERVED AND FRESH MATERIAL

Studies of the structure of the ileocecal junction were made using 61 relatively fresh postmortem specimens; 55 of these were from adults. Twenty of the ileocecal junctions resembled a papillary structure, while forty-one had a variable type of valvular structure. In the five neonatal specimens the valve was papillary in each case. Mechanically, they were competent and, with distention, the frenular structure became apparent.

The oblique approach of the terminal ileum into the cecum was noted in all specimens. Because the ileum and cecum at that point are both invested in the same serosa and sharp dissection is required to separate this common investment, we have called this, for convenience, the tangential measurement of ileum and cecum. When it is dissected free, the ileum then makes a more direct entrance into the cecum (Fig. 8).

We repeated Rutherford's work in dissecting and describing the ileocecal valve in fixed specimens, removed from 16 preserved cadavers. These were fixed undistended preparations in adults without abdominal disease. The preservative used was a phenol-glycerin mixture (phenol, 15%; water, 15%; propylene glycol, 70%) with no formalin. This mixture supposedly fixes

Fig. 6.—X-ray of ileocecal orifice in vivo.

Fig. 7.—Photograph of ileocecal orifice in dog.

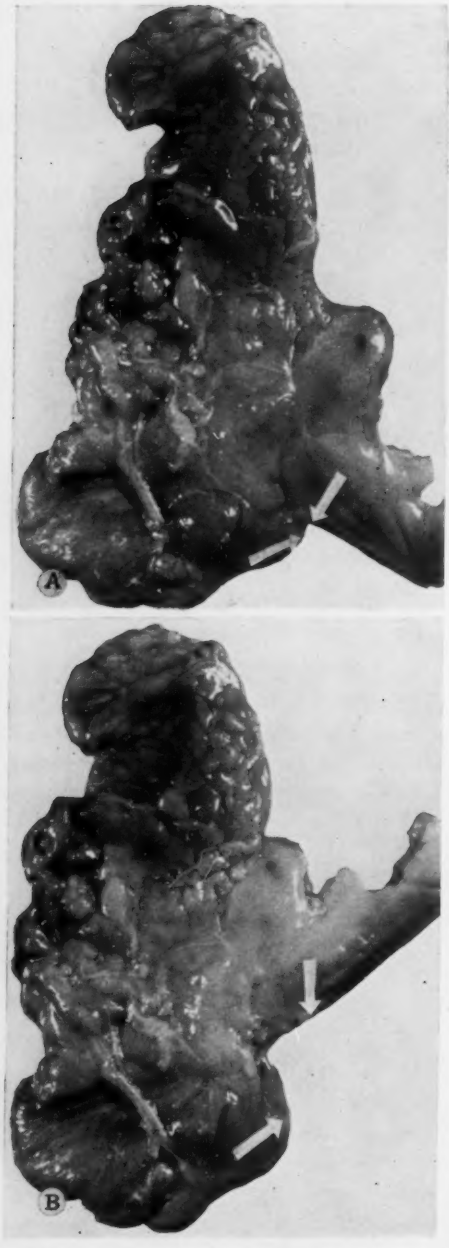

Fig. 8.—Arrows indicate degree of dissection needed to separate ileocecal junction on mesial aspect of cecum with common serosal investment. *A*, before dissection; *B*, after dissection.. Half the distance between the separated arrows was designated "tangential measurement." Fresh postmortem specimen from 68-year-old woman; cecum small, tangential measurement 3.2 cm.

TABLE 3.—*Average Findings in Sixteen Ileocecal Segments Removed from Preserved Cadavers*

A	Length of valve, 2.38 cm.
B	Length of orifice, 1.8 cm.
C	Projection of superior valvulae, 0.86 cm.
D	Thickness, 0.22 cm.
E	Projection of inferior valvulae, 0.5 cm.
F	Thickness, 0.16 cm.
G	Distance from ileocecal orifice to appendicular orifice, 3.14 cm.
H	Tangential measurement of ileum and cecum, 1.44 cm.

elastic tissue with little distortion. The cadavers were kindly offered for study by Dr. O. V. Batson, Graduate School of the University of Pennsylvania. All specimens were in excellent state. The cecum was normal and well developed in each case, averaging 7×6 cm. Table 3 summarizes the average findings in the 16 cadavers. In no case were the inferior valvulae defective; the preparations were entirely similar to those described in the literature. The orifice was in many instances slit-like, guarded by the labia, supported by frenula.

Of the 55 fresh adult preparations, 51 had the well-developed adults' cecum (six cases had had an appendectomy). Of the 61 valves, 20 were papillary in formation, resembling more what we observed in vivo. Forty-one had a valvular or bilabial structure (Table 4). One case grossly had no inferior valvulae. However, histological section revealed the complex musculature layer described by DiDio, indicating that the structure was physiologically not incomplete. One case (Fig. 1) had a well-developed cusp leaflet at the lateral commissure of the orifice. In all preparations, the terminal 2.5 to 7 cm. of ileum was tangential and fused to the mesial cecal wall. The mean of the tangential measurement of the fixed speci-

TABLE 4.—*Observations on Fifty-Five Fresh Postmortem Adult Ileocecal Segments*

A	Length of valve, 3.1 cm.
B	Length of orifice, 2.1 cm.
C	Thickness of valvulae, 0.54 cm.
D	Ileocecal orifice to appendicular orifice (27 cases), 5.51 cm.
E	Tangential measurement of ileum and cecum, 4.25 cm.

mens was 1.43 cm., with a standard error of mean of 0.15 cm. The mean of the fresh specimens was 4.24 cm., with a standard error of 0.18 cm. This was a statistically significant difference, with a probability of coincidence of less than 0.001.

Thus, fixation of the ileocecal preparations with preservatives has a marked effect on the gross appearance of the valvular structure. The orifice becomes more slit-like, and the valvulae or lips become much thinner and the frenular structure is exaggerated. In comparison with the relatively fresh postmortem material, the distance from the ileocecal orifice to the appendicular orifice is reduced, as may be seen by comparing the averages, from 5.51 cm. to 3.14 cm.

Of the 71 adult ileocecal preparations, only three had poorly developed ceca. This agrees with the observations of most anatomical texts that about 90% to 95% are fully developed. Of the 76 preparations that we studied, only 1 had grossly an absent inferior valve leaflet. Histologically, this defective area seemed to have a fairly complete sphincter muscle layer. (Buirge,[6] 3 absent lips in 500 cases.) One case had a commissural valve cusp.

III. COMPETENCE

To help settle the question about the competency of the valve structure we studied the 61 fresh postmortem preparations.

The segments of terminal ileum, cecum, and ascending colon were suspended on a laboratory stand, and a water manometer was attached to the lumen of the cecum. In about one-half of the cases the specimens were not washed, the fecal material being expressed from the colon. In some instances the specimens were washed through with tap water from ileum to colon. It was obvious that the more these specimens were handled and the more they were washed and with the passage of time the ileocecal orifice became more patulous and would take whatever position it was allowed to fall into. Water was introduced into the cecum by means of a catheter, and when it was seen to come through the ileum the pressure on the manometer was read in centimeters of water and recorded as the reflux pressure from cecum through the ileocecal valve to the ileum.

Of the 21 papillary valves only 4 had a reflux pressure of less than 10 cm. of water. Of the 40 bilabial valves 25 had a reflux pressure of less than 10 cm. and 11 of these were absolutely incompetent to water. The valves that had a papillary structure were usually in patients who had sudden deaths or died from an acute illness. The time after death was in most cases from four to seven hours. However, this was not always the case. One patient had carcinoma of the pancreas, and there were three instances in which the preparation was studied 19, 17, and 23 hours after death, respectively. Those preparations that were bivalvular were usually those studied 10 to 14 hours after death and often were from patients with wasting illness. Was there any relation of incompetence to tangential measurements? None could be determined. The frenula (2.5 to 7 cm.) were well developed in half the cases. However, in each instance the orifice was patulous—possibly due to handling or to agonal or postmortem changes.

In summary, the adynamic studies of the valve structures showed a surprising amount of competency. Thus, all the valves of papillary type evidenced a higher degree of competency; the bilabial type of valve was less competent and 11 out of 41 were entirely incompetent. No anatomic reason was available to explain the incompetency.

COMMENT

The combination of a sphincteric papilla plus the anatomic configuration in the normal well-developed ileocecal segment would prompt the conclusion that the ileocecal valve in vivo is hardly ever incompetent at levels of pressure observed clinically. The evidence to date would seem to point out that the structure is papillary and that the valvular components are constructed about this papilla by the oblique entrance of ileum into cecum, by the disposition of the muscle layers of both the ileum and cecum. The frenular structure is more apparent on distention. Our study confirms the observations of DiDio and Fleischner as to the cecal ileum, the part of the terminal ileum that is fused to the mesial cecal wall. There is an obvious disparity in the measurements

and anatomical architecture of fixed specimens when compared with relatively fresh but unpreserved specimens.

We know from roentgenological studies with barium enemas that the majority of these valves can be forced open. Dr. J. S. Lehman,‖ in our x-ray department, estimated that in 70% of the cases barium can be made to flow easily into the ileum at pressures of about 90 cm. of water. In another 25% of the cases the pressure has to be raised well above 90 cm. In 3% to 5% of the cases no amount of pressure or manipulation is able to force the valve open from cecum to ileum. These pressures of course far exceed what is seen clinically, even in large bowel obstruction. Dennis,[31] in a series of cases of large bowel obstruction, reported an average pressure of 14 cm. of water. Sperling [25] reported 10 to 51 cm. of pressure in 12 cases of colon distention. Fleischner [17] reported 90% incompetent to barium enema; also, spot films showed an orifice usually 2 to 3 mm. in diameter. It is probable that with large bowel obstruction there is some degree of reflux. Just how much and how continually would be difficult to estimate. On the other hand, there is evidence suggesting that the ileocecal valve in colon obstruction may prevent emptying of the small intestine. This seems to be a more plausible explanation of the associated small bowel distention than copious reflux from cecum to ileum through an incompetent valve.

The clinical implications are that most completely obstructed colons are not only closed loop obstructions but because of continued emptying of ileal contents into the cecum become "tension closed loops." In our experience, at least 90% of these will require early surgical decompression. Whatever the cause of the associated small bowel obstruction picture—partial reflux, sphincter spasm, tension of distended cecum against the cecal part of the terminal ileum, reversal of peristalsis and pressure gradients, we must reckon with this clinical component of large bowel obstruction. A regimen to include absolutely nothing by mouth and short or long tube suction will not only help correct the condition of small bowel distention but will also break or prevent the pressure gradient causing small intestine emptying into the obstructed colon.

‖ Lehman, J. S.: Personal communication to the authors.

CONCLUSIONS

Observation of the ileocecal orifice in vivo in a very limited number of cases reveals that it is really a muscular papilla projecting into the colic lumen at the junction of cecum and ascending colon. Its behavior is that of a sphincter.

In one patient in vivo observation of the papilla was compared with immediate postmortem appearance. Within 55 minutes the firm papilla became patulous and flatter and tended towards the bilabial configuration.

Roentgenologic observations in some instances confirm the in vivo appearance of a papilla. On distention with barium and with a pressure ring device, the valvular structure is depicted.

Anatomic studies of preserved specimens indicate that the papillary structure is associated with a well-developed valvular architecture.

Study of unpreserved relatively fresh postmortem specimens indicated the following:

(*a*) Fixatives and preservatives distort the cecum and valvular structure.

(*b*) Hydrodynamic studies reveal a surprising amount of competence; however, 18% of specimens were incompetent to water. No anatomic reason was apparent to explain this.

(*c*) The cecal part of the terminal ileum is fused in a tangential fashion with the mesial cecal wall before it actually joins with the layers of the cecal musculature to project into the lumen as a muscular papilla.

(*d*) Grossly, an absent inferior valvula is uncommon.

The nomenclature should reflect accurately the physiologic and anatomic aspects;

"ileocecal valve" is a term widely used, but it should connote the following:

(*a*) "Iliocecocolic papilla" containing a complex sphincter mechanism.

(*b*) "Ileocecocolic valve" of variable anatomical structure grossly complete in over 50% and probably histologically complete in nearly all cases.

(*c*) The "cecal ileum" that has sphincter properties and is anatomically part of the valvular mechanism.

In vivo, the ileocecal papilla and valve probably function together in health in such a way that there is no incompetence. During a barium enema with relatively high pressures (±90 cm. of water) and with local pressure manipulation, the ileocecal orifice can be made incompetent in about 90% of the cases.

This study suggests that

(*a*) Many more observations of the ileocecal papilla should be made through a sigmoidoscope by those who have the opportunity.

(*b*) More extensive anatomic and histologic examinations of the cecal ileum should be made in unpreserved preparations.

In acute large bowel obstruction there is no real evidence about the degree and frequency of incompetence of the ileocecal orifice. We could judge from all evidence available, experimental and clinical, that the mechanism is not continuously incompetent and that nearly always the obstructed colon is a closed loop. The associated picture of small bowel distention seen in about 25% of the cases is probably due to dysfunction of the emptying mechanism of the terminal ileum and not to any significant degree of colic reflux.

SUMMARY

Three more cases of in vivo observations with photographs of the ileocecal papilla in man are presented.

Changes from the observed in vivo appearance of the ileocecal papilla occur almost immediately after death.

Dissection of preserved specimens reveals the valvular structure of the ileocecal orifice.

Dissection of unpreserved fresh postmortem specimens reveals an important part of the valvular structure, the fusion of the terminal 3 to 7 cm. of ileum with the mesial cecal wall. Comparison with preserved specimens indicates that this measurement is markedly contracted by preservation and fixation. This anatomic finding is not generally appreciated in textbooks of anatomy.

Hydrodynamic studies of unpreserved ileocecal valves reveal a surprising degree of competency to water; 18% are incompetent.

In vivo observations in man and dog and studies of preserved and fresh postmortem preparations indicate that the ileocecocolic orifice is made up of a muscular papilla surrounded by a valvular mechanism of rather complex and variable structure.

The anatomical view of "valve" and physiologic view of "sphincter" are compared and related.

The anatomic and physiologic functions of the ileocecocolic segment are of importance in the clinical considerations of acute large bowel obstruction.

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Myocardial Infarction: Changing Sex Ratio and Other Factors

An Epidemiological Study of Acute Myocardial Infarction Based on the Experiences of Barnes Hospital for Forty-Five Years

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From the epidemiological standpoint, certain impressions concerning myocardial infarction are widely held. The incidence of myocardial infarction (1) varies considerably in different parts of the world *; (2) has increased in recent years † and this increase is related to some changing factors in our civilization, such as the consumption of fats, dairy products, or tobacco ‡; (3) is much higher in men than in women §; (4) reaches a peak at a later age in women than in men [13]; (5) is higher in white people than in Negroes ||; (6) is higher in the upper socioeconomic groups than in the lower [4]; (7) is higher among persons with diabetes mellitus than among nondiabetics.# Even though these impressions are widely held, more data are needed in most instances to evaluate their status adequately.

An extensive study of the epidemiological aspects of acute myocardial infarction based on autopsied patients and representing the experiences of a general hospital in the United States over a long period of time has not been made in recent years. Such a study should provide additional data that would be helpful in evaluating some of the epidemiological aspects of myocardial infarction.

Consequently, a survey has been made based on all autopsies of patients from Barnes Hospital performed in the pathology department of Washington University during the years 1910 through 1954. These autopsies include 8183 adults (over 20 years of age). Acute myocardial infarction was a principal diagnosis in 500 of these adults.

Barnes Hospital is a large (820 beds) general hospital in midwestern United States, serving people of all economic classes in St. Louis and in the surrounding areas.

MATERIAL AND METHODS

Data were obtained from the autopsy and clinical records of Barnes Hospital and the department of pathology of Washington University. An attempt was made to characterize the autopsy population and the general hospital admissions by recording such data as age, sex, race, and economic status. Patients with histologic evidence of acute myocardial infarction were placed in a separate group and similarly characterized. An additional group from which data were obtained was composed of all patients (living or dead) with a clinical diagnosis of acute myocardial infarction for the periods 1942-1943 and 1947-1952 (eight years).

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* References 1-4 and Kimura, N.: Analysis of 10,000 Postmortem Examinations in Japan, read before the Second World Congress of Cardiology, Washington, D. C., Sept. 13, 1954.

† References 1, 3, and 5-7.

‡ References 1, 8, and 9.

§ References 3, 7, and 10-12.

|| References 14 and 15.

References 1, 3, and 16.

Fig. 1.—Incidence of acute myocardial infarction in males and females by periods. The percentage plotted for each sex is the percentage of the total adult autopsies of that sex for the period indicated.

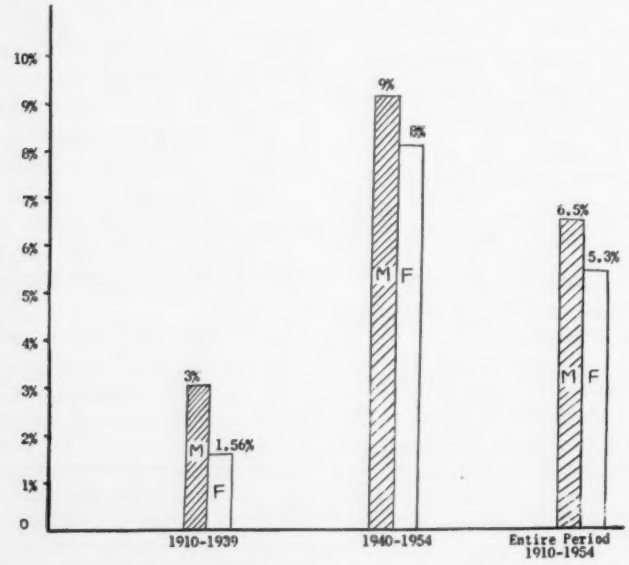

Fig. 2.—Incidence of acute myocardial infarction in the two sexes before and after 1940 and in the entire period 1910-1954. The figures are the percentage of autopsied patients with acute myocardial infarction among the entire autopsies for the sex and period designated.

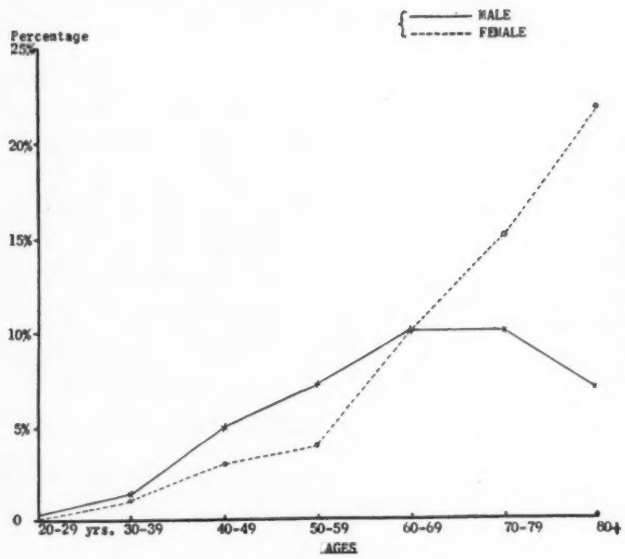

Fig. 3.—Incidence of acute myocardial infarction among total adult male and female autopsies by age. The percentage plotted for each sex is the percentage of the total adult autopsies of that sex for the age group indicated.

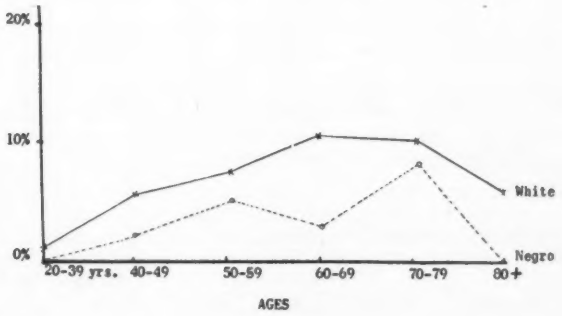

Fig. 4.—Comparison of percentage of white persons and Negroes in each age group with acute myocardial infarction.

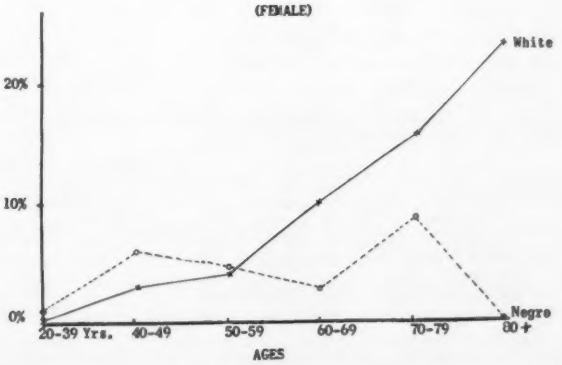

TABLE 1.—*Age, Sex, and Race of 500 Consecutive Autopsied Patients with Acute Myocardial Infarction*

	Male			Female			Total	
Age, Yr.*	White, No.	Negro, No.	Total, % of Total Males (334)	White, No.	Negro, No.	Total, % of Total Females (166)	Total No.	% of Total (500)
20-29	1	0	0.3	0	0	0.0	1	0.2
30-39	8	0	2.4	3	2	3.0	13	2.6
40-49	45	2	14.4	15	5	12.6	68	13.6
50-59	87	5	27.5	25	3	16.8	120	24.0
60-69	115	2	35.0	53	1	32.5	171	34.2
70-79	56	2	17.4	43	1	26.5	102	20.4
80+	10	0	3.0	15	0	9.0	25	5.0
Totals	322 (96.4%)	12 (3.6%)	66.8 of 500	154 (92.7%)	12 (7.3%)	33.2 of 500	500	100.0 of 500

* Average age of males, 61 years; of females, 64 years.

TABLE 2.—*Age, Sex, and Race of the Total Adult Autopsy Population of Barnes Hospital for the Period 1910-1954 (8,183 Patients)*

	Male			Female				
Age, Yr.*	White, No.	Negro, No.	Total, % of Total Males (5,100)	White, No.	Negro, No.	Total, % of Total Females (3,083)	Total No.	% of Total Autopsy (8,183)
20-29	356	42	7.8	308	72	12.3	778	9.5
30-39	499	78	11.3	412	111	16.9	1,100	13.5
40-49	846	118	18.9	506	83	19.1	1,553	18.9
50-59	1,171	98	24.9	616	73	22.3	1,958	23.9
60-69	1,097	67	22.8	511	34	17.7	1,709	20.9
70-79	565	26	11.6	278	11	9.5	880	10.8
80+	131	6	2.7	65	3	2.2	205	2.5
Totals	4,665 (91%)	435 (9%)	62.3 of 8,183	2,696 (87.4%)	387 (12.6%)	37.7 of 8,183	8,183	100.0 of 8,183

* Average age of males, 54 years; of females, 47 years.

TABLE 3.—*Total Adult Autopsies and Incidence of Acute Myocardial Infarction by Periods*

	Total Autopsies			Cases with Acute Myocardial Infarction, No.			Cases with Acute Myocardial Infarction, %		
Year	Total	Male	Female	Total	Male	Female	Total	Male	Female
1910-1919	407	267	140	2	2	0	0.5	0.7	0.0
1920-1929	1,085	673	412	17	14	3	1.6	2.0	0.8
1930-1939	1,876	1,161	715	64	47	17	3.4	4.0	2.3
1940-1944	1,343	868	475	61	41	20	4.5	4.7	4.5
1945-1949	1,534	966	568	158	102	56	10.3	10.5	9.8
1950-1954	1,938	1,165	773	198	128	70	10.1	11.0	9.0
Total 1910-1954	8,183	5,100	3,083	500	334	166	6.1	6.5	5.3

TABLE 4.—*Incidence of Acute Myocardial Infarction by Age, Sex, and Periods*

	Incidence of Myocardial Infarction, %*											
	20-39 Yr.		40-49 Yr.		50-59 Yr.		60-69 Yr.		70-79 Yr.		80+ Yr.	
Year	M	F	M	F	M	F	M	F	M	F	M	F
1910-1919	0.0	0.0	0.0	0.0	0.0	0.0	12.0	0.0	0.0	0.0	0.0	0.0
1920-1929	0.8	0.0	2.3	1.3	4.5	0.0	4.4	5.2	0.0	0.0	0.0	0.0
1930-1939	0.4	0.4	4.3	3.0	5.7	3.0	8.7	6.6	8.3	10.3	0.0	0.0
1940-1944	1.3	0.9	5.6	5.9	4.5	5.0	6.0	3.3	9.5	15.0	5.0	9.0
1945-1954	2.5	0.8	7.8	5.6	12.4	6.7	17.0	14.8	13.0	18.8	22.0	37.5

* The figures given are the percentages of the total adult autopsies of the age, sex, and periods indicated.

RESULTS

The results are presented in detail in Tables 1 to 5 and Figures 1 to 4.

Autopsies were performed on 500 patients from Barnes Hospital with histologic evidence of acute myocardial infarction during the period January, 1910, to November, 1954. Of these 500 patients, 334 (66.8%) were men and 166 (33.2%) were women. The average age of the men was 61 years, and that of the women, 64 years; 95.2% were white and 4.8% were Negro. There was a clinical diagnosis of diabetes mellitus in 19.6% (13.7% of the 334 men and 31.3% of the women). Private patients comprised 65%, and 35% were ward (charity and partial payment) patients. The incidence of acute myocardial infarction in the Barnes Hospital autpsy series increased from 0.5% (2 in 407 autopsies) in the decade 1910-1919 to 10.2% in the decade 1945-1954 (356 in 3472 autopsies). The increase occurred in all age-groups, as shown in Table 4.

TABLE 5.—*Sex, Race, and Economic Status of All Groups*

	Total Hospital Admissions,* %	Total Autopsies on Adults,† %	Clinical Diagnosis of Acute Myocardial Infarction,‡ %	Anatomical Diagnosis of Acute Myocardial Infarction,§ %
Sex				
Male	50.7	62.4	71.2	66.8
Female	49.3	37.6	28.8	33.2
Race				
White	86.8	90.0	95.0	95.2
Negro	13.12	10.0	5.0	4.8
Other	0.08	....	....	....
Economic status				
Ward	31.0	40.0	25.7	35.4
Private	69.0	60.0	74.3	64.6

* Period of 12 years, 1942-1953. Total of 233,275 admissions, excluding obstetrical patients and children.
† Period of 45 years, 1910-1954. Total of 8,183 adults.
‡ Total period eight years, 1942-1943 and 1947-1952. Total of 1,399 patients.
§ Period of 45 years, 1910-1954. Total of 500 patients.

The entire autopsy population over 20 years of age from Barnes Hospital for the period 1910-1954 consisted of 8183 patients; 62.4% were men and 37.6% were women. The average age of the entire group was 51 years; that of men was 54 years, and that of the women, 47 years. The average age of men in the decade 1910-1919 was 48, and that of women, 42. The average ages increased progressively, until in the decade 1945-1954 the average age of the men was 57 and that of the women was 53. Of the entire group, 90% were white and 10% were Negro. The private patients comprised 60%, and 40% were ward patients. A clinical diagnosis of diabetes mellitus had been made in 5.1% of cases in the last 4000 autopsies (4.1% of the men and 7.1% of the women).

Data on total admissions to Barnes Hospital for the entire period 1910-1954 were not available, but data for the 12-year period 1942 through 1953 were available. During this period there were 233,275 admissions (excluding obstetrical patients and children); 50.7% were men and 49.3% were women; 86.8% were white and 13.2% were Negro; 69% were private and 31% were ward patients.

Data on all patients in Barnes Hospital with a clinical diagnosis of acute myocardial infarction were available for the periods 1942-1943 and 1947-1952 (eight years). During these periods there were 1399 patients with such a clinical diagnosis; 71.2% were men and 28.8% were women. The average age was 59.4 years; 95% were white and 5% were Negro; 74.3% were private and 25.7% were ward patients.

COMMENT

Geographical Aspects.—The extent of differences in the incidence of myocardial infarction in various geographical areas is not easy to determine because of the difficulty in establishing suitable groups for comparison. Among factors which must be considered are the following: (1) age distribution in population, (2) reliability of diagnoses, (3) local customs regarding medical care and hospitalization. In general, autopsy diagnoses provide a more satisfactory basis for comparison than clinical diagnoses because the reliability of clinical diagnoses varies widely in different geographical areas and, even in areas with high medical standards, clinical diagnoses are not always accurate. However, an autopsy population is a selected one, and

it is necessary to know to what extent it reflects the general population. Even with the data available in a large medical center in the United States, we cannot with certainty determine this relationship. Even so, data from this institution do provide some basis for comparison with data from similar institutions in other parts of the world. Davies,[2] in East Africa, reported the rarity of atherosclerosis and any of its complications in a series of 2804 adult autopsies. Only 760 of his autopsied patients were over 40 years of age, but even in the latter group the rarity of atherosclerosis would seem to be significant. Kimura,* of Kyushu, Japan, found a low incidence of myocardial infarction (acute and healed approximately 1%) among 10,000 autopsies. In order to satisfactorily compare this figure with our own data, we need to know at least (1) the percentage of patients with acute myocardial infarction, (2) the age and sex distribution in the autopsy series, (3) the local customs regarding hospitalization of patients with acute myocardial infarction during the period covered by the autopsy series. Superficial comparison of the currently available figures suggests that the incidence of myocardial infarction in the Kyushu series is similar to that in the St. Louis series in the period 1910-1930 and is much less than in the current period.

In a series of 2967 autopsies (mostly adults) at the Massachusetts General Hospital, Boston,[3] performed between 1933 and 1940, 105 cases of acute myocardial infarction were found, an incidence of 3.5%. This is similar to the incidence of 3.4% for our series in the period 1930-1939.

In a series of 30,265 autopsies (including persons of all ages except newborn infants) performed at the University of Minnesota during the period 1910 to 1938, Clawson [11] found 1215 whose deaths were attributed principally to coronary arteriosclerosis. This is an incidence of 4%. The incidence of acute myocardial infarction among adult autopsies at Barnes Hospital during this period is 2.5%. The figures of incidences in these two series cannot be compared directly, since one includes all age groups and the other only adults and since one includes all patients whose deaths were attributed to coronary arteriosclerosis and the other only those who died from acute myocardial infarction.

Increasing Incidence.—There was a 20-fold increase in the incidence of myocrdial infarction in the decade 1945 through 1954 compared with the decade 1910 through 1919. The difference is also striking between the incidence of acute myocardial infarction in the entire first 30 years, 1910-1939 (83 in 3368 adult autopsies), compared with the last 10 years, 1945-1954 (356 in 3472 adult autopsies).

A portion of this increase in incidence of acute myocardial infarction in the Barnes Hospital autopsy series may be due to the recent trend toward more frequent hospitalization of patients with suspected myocardial infarction.

A portion may be explained by the increasing proportion of the population that survives to an older age. There was a slight rise in average age of the adults in the autopsy population during the period studied. However, when the entire autopsy population is divided into age groups for each of five periods from 1910 to 1954 and the percentage of patients with acute myocardial infarction determined for each division (Table 4) it is apparent that a rise in incidence has occurred in all age groups.

It seems unlikely that errors in anatomical diagnoses account for a significant portion of the increase in incidence in this autopsy series. The possibility was considered that some cases of acute myocardial infarction were misdiagnosed as acute myocarditis in the early years. However, less than half a dozen diagnoses of myocarditis were made, and reexamination of the microscopic sections from these failed to substantiate a diagnosis of acute myocardial infarction.

* Kimura, N.: Analysis of 10,000 Postmortem Examinations in Japan, read before the Second World Congress of Cardiology, Washington, D. C., Sept. 13, 1954.

It is possible that the increase in incidence of acute myocardial infarction in the autopsy population reflects, at least in part, a real increase in the general population. Evidence derived from several other sources also indicates that there has been an increase in incidence of coronary arteriosclerosis and acute myocardial infarction in recent years in the United States. Charts based on data obtained from the Bureau of Vital Statistics indicate that the death rate from arteriosclerosis increased twofold from 1935 to 1947,[1] and this rate of increase is almost identical with the rate of increase in the Barnes Hospital autopsy series for the same period. The incidence of coronary occlusion and acute myocardial infarction as a cause of death among physicians in the United States has increased considerably in recent years, as determined by examinations of the causes of death listed in the obituary section of *The Journal of the American Medical Association*. The incidence of coronary occlusion and acute myocardial infarction among 1000 physicians listed consecutively in the obituary section of *The Journal of the American Medical Association* in 1940 was 19.5%, and among a similar consecutive group in 1953 the incidence was 28.5%. These figures on physicians have the disadvantage of being derived from a single specialized group, but it seems likely the clinical diagnoses made on physicians would be more reliable than on any other group in the general population.

If there has been a real increase in the incidence of acute myocardial infarction, it may be due to changing factors in our modern civilization. For example, the consumption of tobacco increased tremendously in the period 1910 to 1954. The consumption of cigarettes in the United States among persons 15 years of age and over in 1920 was 620 per person, and the corresponding figure in 1953 was 3500 (456% increase).[8] It seems reasonable to assume that the consumption of cigarettes by women during this period increased more than the consumption by men. The ratio of the incidence of men with acute myocardial infarction in the Barnes Hospital autopsy population to women with a similar diagnosis was 2:1 for the period 1910 through 1939. The corresponding ratio for the period 1940 through 1954 was 1.1:1. No conclusions are warranted, but it is certainly interesting that the change in ratio between men and women with acute myocardial infarction in our autopsy period changed during a period in which the ratio of women who smoked to men who smoked very likely also changed. Using an entirely different approach, Hammond and Horn[8] demonstrated a relationship between smoking habits and death rates from coronary arteriosclerosis in a follow-up study of 187,766 men.

According to figures obtained from the National Dairy Council,[17] the consumption of dairy products per person in the United States has not changed markedly during the period 1910 to 1954 (748 lb. total milk consumption per person in 1910 and 689 lb. in 1953). Thus it seems unlikely that the consumption of dairy products is related to the apparent increase in the incidence of acute myocardial infarction.

The total fat consumption in the American diet increased gradually from 31.8% of the total caloric intake in 1910 to 38.3% in 1940 and 40.2% in 1950.[9] It has been suggested[9] that this increase in the consumption of fat is associated with the apparent increase in incidence of arteriosclerosis.

Of course numerous other factors in our modern civilization have also changed, and the mere fact that a factor has changed is obviously insufficient to incriminate it as a factor in the production of arteriosclerosis. Further evidence from numerous other sources (such as that derived from experimental animals) is required.

Factor of Sex.—Among the most remarkable data obtained from the Barnes Hospital series are those regarding the incidence of acute myocardial infarction in the two sexes. When the proportion of males to females in the entire autopsy series is taken into consideration, the incidence of acute myocardial infarction in the two sexes differs only slightly (6.5% for men and 5.3% for women, which is a ratio of 1.2:1).

The similarity of these figures contrasts sharply with the difference in the incidence in the two sexes reported in numerous other series † based on clinical data (others have reported a preponderance of the disease in men, with the ratio of men to women varying from 3:1 to 7:1). Even in our own series (see Table 5) based on clinical diagnoses, the ratio of the incidence between the two sexes was 2.4 males to 1 female (hospital admissions exclusive of obstetrical patients were evenly divided).

The only large autopsy series from which data on the incidence in the two sexes are available for comparison is based on the period 1910-1938. Among 30,265 autopsies performed at the University of Minnesota during this period (1910-1938), Clawson [11] found the ratio of incidence between the two sexes was 2.5 males to 1 female (50 men died from coronary arteriosclerosis per 1000 autopsies performed on males; the corresponding figure for women was 20). In the Barnes Hospital autopsy series for the period 1910-1939 the ratio of incidence of acute myocardial infarction between the two sexes was approximately 2 males to 1 female (Fig. 2). This difference is highly significant (p=less than 0.01). However, since 1940 the ratio has changed and approaches 1 male to 1 female (actually, 1.1 to 1, which is not a significant difference in this series, since p=0.3). Since most of the patients were from the period 1940-1954, the ratio of incidence between the two sexes for the entire period 1910-1954 was 1.2 males to 1 female, which indicates only a slight difference, although this difference between incidences is significant in this series (p=0.05).

There seems little reason to doubt that prior to 1940 the ratio of incidence of coronary arteriosclerosis and acute myocardial infarction in the two sexes was actually at least 2 males to 1 female. Evidence from all sources, including our own autopsy series supports this conclusion. If this ratio has actually changed in the general population since 1940 to 1:1, as it has in the Barnes Hospital autopsy series, it is of profound significance. More data from other sources, particularly from other autopsy series, are needed for final evaluation.

Factor of Age in Males and Females.—The data derived from this series indicate that the incidence of acute myocardial infarction in females is proportionately greater in the older age groups than in males. Similar observations have been reported by others.[13] It is noteworthy that the incidence of acute myocardial infarction in women rose steadily with age but that it became stationary in males from 60 to 80 years of age, then decreased after 80 (Fig. 3). These data are compatible with the hypothesis [1] that female hormones inhibit the development of arteriosclerosis, since they decrease progressively with age.

Racial Incidence.—The number of Negroes in the Barnes Hospital autopsy series is so small that definitive conclusions are not warranted. However, the incidence of acute myocardial infarction was considerably lower (in almost all age groups, as shown in Figure 4) in the 822 autopsied Negroes (2.9%) than in the 7361 white persons (6.4%), and this difference is statistically significant (p<0.01). A similar difference in racial incidence has been noted by others.‡

Economic Status.—The socioeconomic status of the patients does not appear to have been an important factor in the incidence of acute myocardial infarction in the Barnes Hospital autopsy series, since the incidence was similar in ward patients (partial payment or charity) and private patients. Results from other studies [4] have suggested that the incidence is considerably greater in the higher economic groups. Also, results from our own studies at Barnes Hospital based on clinical diagnoses (Table 5) have indicated that the incidence was considerably higher among private patients. The explanation for the discrepancies between the two types of data is not clear. Acute myocardial infarction may be fatal more frequently in

† References 12 and 15-17.

‡ References 1, 14, and 15.

poorer persons, since it is possible that they seek medical care at a later stage than the well-to-do persons.

Diabetes Mellitus.—The results of the survey of the Barnes Hospital autopsy series support the concept § that diabetes mellitus is an important factor in the development of arteriosclerosis, particularly in women. Diabetes mellitus was more than four times as common among women with acute myocardial infarction as among women in the general autopsy population. Among men with acute myocardial infarction, diabetes mellitus was more than three times as common as it was among men in the general autopsy population.

SUMMARY

Data pertaining to some epidemiological aspects of acute myocardial infarction (based on a study of 500 autopsied patients with acute myocardial infarction) were obtained from a survey of the autopsy and clinical records of Washington University and Barnes Hospital, covering the period 1910-1954.

The data obtained and conclusions drawn can be summarized as follows:

Geographical Aspects.—The incidence of acute myocardial infarction has been established in a large autopsy series (500 among 8183 adults) as a basis for comparison with other similar groups. The incidence is similar to that derived from a smaller series at the Massachusetts General Hospital, in Boston, and is considerably higher than that reported from the Orient and Africa. More data from these other parts of the world are needed before definitive conclusions can be drawn.

Increasing Incidence.—The incidence of acute myocardial infarction has increased tremendously in all age groups in this autopsy series in the last 45 years. The incidence is 20 times greater in the decade 1945-1954 than in the decade 1910-1919. This increase is explained at least in part by the changing character of medical care and illustrates the necessity of taking into account the local customs regarding medical care in analyzing data from other parts of the world. However, the increase may reflect in part an actual increase in the incidence of the disease in the population and may be related to some changing factors in our civilization.

Factor of Sex.—The most remarkable observation made is that the incidence of acute myocardial infarction in the two sexes differs only slightly when the proportion of males to females in the entire autopsy series is taken into consideration (1.2 males to 1 female). Even more remarkable is the observation that a change in this ratio occurred about 1940. For the period 1910-1939 the corresponding ratio was 2:1. For the period 1940-1954 it was 1.1:1. The fact that there were more patients with acute myocardial infarction in our autopsy series after 1939 than prior to 1939 accounts for the 1.2:1 ratio for the entire period 1910-1954.

Factor of Age.—The data obtained from this series support previous observations indicating that the peak of incidence occurs later in females than in males.

Racial Incidence.—The incidence is proportionately higher in white persons than in Negroes in this series.

Economic Status.—The socioeconomic status of the patients in this series does not appear to have been an important factor.

Diabetes Mellitus.—Diabetes mellitus was much commoner among patients with acute myocardial infarction than it was in the general autopsy population.

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Sinus Disease, Bacterial Allergy, and Bronchial Asthma

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The intrinsic form of bronchial asthma remains an enigma. For some it signifies asthma of unknown cause, preferably termed "idiopathic"; to others it is largely a psychosomatic problem, but for many it is still almost wholly equated with "bacterial" or "infective" asthma. At the heart of the last concept lies the question of the relationship of sinus infection to bronchial asthma, which persists as a matter of controversy. This report is offered in the hope of clarifying the issues involved in this problem.

Four years ago a clinical research unit, including an allergist and a bacteriologist, was organized in the department of otolaryngology at the Mount Sinai Hospital, to investigate the subject of focal infection [1] as it concerns the role of nasal and sinus disease. This group met one morning a week for three years. Bronchial asthma constituted the largest group of cases studied, and these comprise the case material of this report.

In this study the attempt was made to employ more precise and bacteriologically valid criteria to determine the presence or absence of infection, as previously described by Goldman.* This method involves a correlation of the observations of cultures and spreads of secretion. Much of the confusion surrounding the role of the paranasal sinuses in "focal infection" and in "bacterial allergy" has derived from the failure to distinguish carefully between true infection of the sinuses, and sinus disease not due to infection. Too much reliance has been placed upon x-ray findings alone, so that all alterations of sinus membrane were considered indicative of sinus infection. There has been a frequent misinterpretation placed upon the gross character of the return from diagnostic sinus lavage. The tendency has been to assume that large amounts of secretion, grossly mucoid, mucopurulent, or purulent in appearance, were inevitably evidence of infection.

To establish the existence of true sinus infection it is essential to demonstrate the presence of actual or potential pathogens in the sinus secretions and to find indication of their active multiplication. It is by no means uncommon that sinus secretion is found to contain only nonpathogens on culture, although its gross appearance alone would suggest infection. Direct spreads of such specimens often show large amounts of mucus; many eosinophiles, 25% or more, and a paucity or absence of micro-organisms. Conversely, it is possible to find pathogens with many colonies on blood plates cultured from scant thin secretion or flakes. Sinus secretion of true infection shows many polymorphonuclear cells on direct spread, but even more, and of much greater diagnostic significance, the presence of many micro-organisms.

It may be helpful to define our use of the terms pathogenic, potentially pathogenic, and nonpathogenic micro-organisms. Diplococcus pneumoniae, hemolytic Streptococcus, Hemophilus influenzae and parainfluenzae, and Klebsiella pneumoniae are considered pathogenic even when isolated in small numbers

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* References 2 and 3.

from nasal or sinus secretion. Micrococcus pyogenes var. aureus (Staphylococcus aureus) Type A, viridans Streptococcus, nonhemolytic Streptococcus, Bacillus proteus, and Pseudomonas aeruginosa are potentially pathogenic and are considered pathogenic only when found persistently or in moderate to large numbers. Micrococcus pyogenes var. albus (Staphylococcus albus), Staphylococcus aureus B, diphtheroids, and Neisseria pharyngis are, as a rule, nonpathogenic.

MATERIAL AND METHODS

One hundred nine asthmatic patients were referred to the research clinic for study of foci of infection in the nose and sinuses. Most of these patients were referred because it was believed that infection in the upper respiratory tract was a causative factor in their asthma. The investigation included in most of the patients roentgen examination, diagnostic lavage of the maxillary antrums and sphenoid sinuses, and cultural and microscopic examination of the nasal, sinus, and nasopharyngeal secretions by the method described by Goldman.

Eighty-two of the cases referred to the clinic had a complete allergic and bacteriologic study and are included in this report. Fifty-eight patients showed no evidence of clinical sensitivity.† Their skin tests were either completely negative or gave only a few slight positive reactions. They were therefore placed in the group termed "intrinsic asthma."

Twenty-four patients showed definite clinical sensitivity, and their skin tests showed marked positive reactions. They were placed in the group termed "extrinsic asthma."

An additional study was made in a group of 16 patients with intrinsic asthma who showed thickened mucous membrane of the sinuses on x-ray examination. The membranes were removed at radical antrum operations or by trephine biopsy. Cultural and microscopic examinations were made of the sinus secretion preoperatively. The membranes were triturated and cultured on blood agar plates. They were sectioned and prepared both for histological study and for demonstration of bacteria.

A group of 11 patients with intrinsic asthma were tested with subcutaneous provocative injections of autogenous sinus vaccines for the elicitation of asthmatic responses. Forty-five tests were made with 12 vaccines. These were heat-killed suspensions in a concentration of 1,000,000,000 micro-organisms per milliliter.

A follow-up study of sinus surgery in 61 asthmatic patients is included. These patients had been selected for operation because of persistent sinus disease with abnormal membrane. In one group, of 30 cases, sphenoethmoidectomy and intranasal antrotomy were performed. In the second group, of 31 cases, these procedures were supplemented by radical antrum operations.

The technique of obtaining suitable specimens for microscopy and culture has been described previously by Goldman.‡ A sterile platinum loop was applied to nasal membrane in the sphenoethmoidal recess, the middle meatus, and over the turbinates. Copious secretion was aspirated with a sterile pipette. A platinum loop is superior to a cotton swab, as the latter may cause gagging, with resultant contamination from the nasopharynx.

Nasopharynx cultures were obtained by means of a large curved platinum loop carefully passed through the mouth, avoiding contamination with oral mucous membrane. The bacterial flora of the nasopharynx, which has been aptly called "the reservoir for infection," is totally different from that of the nasal cavities.

Secretion from the sinuses was obtained by irrigation through the natural ostium and collected into a basin under surgically clean conditions. Suitable specimens were then aspirated into a sterile pipette for culture and spreads.

Cultures were made directly on blood agar plates, which afford ready identification and a gross quantitative estimate of the number of micro-organisms present. We do not rely on broth cultures, which in the absence of a quantitative factor may prove quite misleading. Spreads were stained for cellular elements and, even more important, for an estimate of the number of micro-organisms and their preliminary identification.

OBSERVATIONS

1. Bacteriology of Sinus Secretion in Asthma

Bacteriologic studies were made on the antral secretions of 82 patients. The secretions were sterile in 12 instances and yielded nonpathogens in 21, potential pathogens in 35, and pathogens in 14 (Table 1).

Among the intrinsic group, of 58 patients, the antral secretion was sterile or showed nonpathogens in 19, yielded potential pathogens in 26, and yielded pathogens in 13. Among the extrinsic group, of 24 cases, the antral secretion showed no micro-organisms or nonpathogens in 14, potential pathogens in 9, and a pathogen in 1.

† Sensitivity to acetylsalcylic acid, present in some instances, played no significant role in the continuing asthma.

‡ References 2 and 3.

On the basis of the cultural and microscopic criteria we have established, 30 of the 82 patients showed evidence of sinus infection (Table 2). Among the 58 intrinsic cases, 25 had sinus infection and 33 were free from infection. Among the 24 extrinsic cases, 5 had sinus infection and 19 were free from infection.

In summary, sinus infection was present in less than half of the intrinsic group and in about 20% of the extrinsic group. The absence of evidence of infection in the majority of intrinsic cases is noteworthy, because infection is frequently offered as the most probable causative factor in this form of bronchial asthma.

TABLE 1.—*Bacteriology of Paranasal Sinuses in Bronchial Asthma*

	Cases, No.			
	Sterile	Non-pathogens	Potential Pathogens	Pathogens
Intrinsic asthma ..... (58 cases)	9	10	26	13
Extrinsic asthma ..... (24 cases)	3	11	9	1
Total (82 cases)....	12	21	35	14

TABLE 2.—*Paranasal Sinus Infection in Bronchial Asthma*

	Cases, No.	
	Without Sinus Infection	With Sinus Infection
Intrinsic asthma (58 cases).....	33	25
Extrinsic asthma (24 cases).....	19	5
Total (82 cases).....	52	30

2. Long-Term Bacteriologic Observations of Sinuses in Asthma

Our study of these asthmatic patients over a three-year period permitted us to make long-term bacteriologic observations in a number of cases, in several of which there had been previous sinus surgery (Table 3). The following are illustrative:

Cases 1 and 2 demonstrate that pathogens may be isolated from the sinuses for a brief period of time and then not be recovered for months thereafter. These cases strongly suggest that such infections were transient in character.

Case 3 illustrates the multiplicity of pathogens which may characterize the sinus flora of asthmatics. In this patient, S. aureus A was repeatedly present over a 10-month period. For a short time Pneumococcus Type 10 was found in two cultures, two weeks apart, and H. parainfluenzae was isolated on another occasion. Then, on four successive observations, neither of these two pathogens could be demonstrated.

In Case 4 three different pathogens were isolated at different times over a period of 22 months.

In Case 5 multiple infection of the sinuses caused by S. aureus A and Pneumococcus Type 25 was present for several months. Antibiotic therapy rid the sinuses of the Staphylococcus, but the Pneumococcus persisted. Hemolytic streptococci then appeared briefly, and for three months thereafter only nonpathogens could be found.

Case 6 shows that a persistent sinus infection can be caused by the same microorganism over a period of two years, in this instance by S. aureus A. On two separate occasions, once for a period of several months, hemolytic Streptococcus was also cultured from the sinus secretion.

The observations indicate the variety of micro-organisms that may inhabit the sinuses in a single case and that they often may be transient rather than permanent residents. This multiplicity suggests a lack of specificity in the relation of the micro-organisms isolated to the underlying membrane pathology and to the continuing asthma. Variations in the bacterial flora of the sinuses were unaccompanied by any change in the asthmatic status. Such findings support the concept that pathogens isolated from the sinuses of asthmatics are often secondary invaders.

3. Correlation of Sinus Radiology with Bacteriologic Evidence of Infection

Seventy-one patients had both complete roentgen and bacteriologic examinations (Table 4). In 15 cases with abnormal

TABLE 3.—*Long-Term Bacteriologic Observations of the Paranasal Sinuses in Bronchial Asthma*

Case	Month of Observation 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	o*	o	..	x* Pneumo. 10	x	o	o	o	o	..	o	o	..	..	..	..	..	..	..	.. Transient infection	..	..	..	..
2	o	o	o	.. Pneumo. 0; Hemolytic Str.	x	..	x Viridans Str.	x	..	o	o	..	..	..	..	..	..	..	..	..	..	..	..	..
3	x Staph. aureus A	..	x Pneumo. 10	x	x H. para-influenzae	x	x Staph. aureus A	x	..	..	..	..	..	..	..	..	..	..	.. Transient infection	..	..	..	..	..
4	o	o	x Pneumo. 8	x	x	x	..	x	..	x	..	x	..	x Hemolytic Str.	x	..	x Pneumo. 11	x	x	.. Multiple infection	x Hemolytic Str.	x	..	..
5	x Viridans Str.	..	x	x Pneumo. 25; Staph. aureus A	x	o Antibiotics	o	o	..	x Pneumo. 25	..	x	x Hemolytic Str.	x	..	o	o	o	.. Multiple infection	..	..	..	..	..
6	x	..	..	..	x x Hemolytic Str.	..	x Staph. aureus A	..	..	..	x	..	..	..	x	.. Hemolytic Str.	.. x	.. x	..	.. Persistent & transient infection	x	..	..	x

* x, pathogens or potential pathogens; o, nonpathogens.

TABLE 4.—*Radiologic and Bacteriologic Findings of Paranasal Sinuses in Bronchial Asthma*

Sinus X-Ray Findings	Cases, No. Sterile	Non-pathogens	Potential Pathogens	Pathogens
Negative (29 cases).	3	8	14	4
Positive (42 cases)..	6	9	20	7
Total (71 cases)	9	17	34	11

TABLE 5.—*Radiologic Findings and Paranasal Sinus Infection in Bronchial Asthma*

Sinus X-Ray Findings	Cases, No. Without Sinus Infection	With Sinus Infection
Negative (29 cases).....	20	9
Positive (42 cases).....	24	18
Total (71 cases).....	44	27

sinus membranes cultures of the sinus washings were sterile or yielded nonpathogens. Equally important is the fact that in 18 cases without abnormal sinus membranes cultures of the sinus washings yielded potential or actual pathogens. When the cases were divided according to the presence or absence of infection of the sinuses, it was found that, of 42 cases with positive x-rays, 18 showed sinus infection and 24, no infection (Table 5). Of 29 cases with negative x-rays, 9 had sinus infection and 20 had no infection.

It therefore appears that thickened membrane of the sinuses may be observed on roentgenograms in bronchial asthma without evidence of sinus infection and, conversely, sinus infection may be present without thickened membranes. Our observations, however, do indicate that sinus infection was more frequent in cases with abnormal membrane findings. This combination of infection and thickened membrane was seen more often in intrinsic asthma than in asthma with detectable allergic factors. We wish to point out that this does not necessarily imply a causal relationship.

4. Bacteriology and Micro-Pathology of Sinus Membranes

These observations are offered tentatively, for, as they concern a small group of cases, they serve chiefly to raise questions rather than to provide answers. The first group, of eight cases, were patients with intrinsic asthma from whom antral membrane was obtained at operation (Table 6). Cultures of membrane yielded no growth in two cases. Preoperative irrigation was sterile in one but grew out P. aeruginosa in the other. Case 3 yielded only S. albus B both from membrane and irrigation. Membrane and irrigation showed a few colonies of S. albus A in Case 4. In Case 5 the membrane yielded only a few colonies of S. albus A, but preoperative irrigation showed both P.

TABLE 6.—*Bacteriology and Micropathology of Paranasal Sinus Membrane in Bronchial Asthma: 1. Antral Membrane Removed at Operation*

	Bacteriology		Pathology	
Case	Preoperative	Membrane	Micro-Organisms	Histopathology
1	No growth	No growth	None	Infiltration with many eosinophiles; edema
2	Pseudomonas aeruginosa, many colonies	No growth	None	Same as Case 1
3	Staphylococcus albus B, few	Staphylococcus albus B, few colonies	None	Same as Case 1
4	Staphylococcus albus A, few	Staphylococcus albus A, few	None	Same as Case 1
5	Pneumococcus, Type 19, moderate colonies; hemolytic Streptococcus, few	Staphylococcus albus A, few	Superficial necrosis with cocci; few cocci beneath basement membrane	Same as Case 1
6	M. catarrhalis; diphtheroids	Viridans Streptococcus, moderate number of colonies	None	Same as Case 1
7	Viridans Streptococcus; Staphylococcus aureus A, moderate number of colonies	Nonhemolytic Streptococcus, moderate numbers	None	Same as Case 1
8	Pneumococcus, Type 19, many colonies	Pneumococcus, Type 19, many	Few cocci beneath basement membrane	Same as Case 1

Type 19 and hemolytic streptococci. Case 6, showing only nonpathogens on irrigation, yielded moderate numbers of viridans streptococci from membrane. In Case 7 irrigation had yielded both viridans Streptococcus and S. aureus A in moderate numbers and nonhemolytic streptococci grew out in moderate numbers from the membrane. Case 8 showed many colonies of Pneumococcus Type 19 from both irrigation and membrane.

Microscopic examination of all eight membranes showed characteristic allergic changes such as infiltration with many eosinophiles, marked edema of the stroma, and thickening of basement membrane. In two only were micro-organisms seen in sections. In Case 5

TABLE 7.—*Bacteriology and Micropathology of Paranasal Sinus Membrane in Bronchial Asthma: 2. Trephine Biopsy of Antral Membrane*

	Bacteriology		Pathology	
Case	Pretrephine	Membrane	Micro-Organisms	Histopathology
9	No growth	No growth	None	Infiltration with many eosinophiles; edema
10	No growth	No growth	None	Same as Case 9
11	B. proteus, many colonies	Stephylococcus albus B, moderate colonies	None	Same as Case 9
12	Aerobacter aerogenes, few colonies	Aerobacter aerogenes, few colonies	None	Same as Case 9
13	Sterile	Staphylococcus aureus A, many	None	Nonspecific acute and chronic inflammation
14	B. proteus, many	B. proteus, many	None	Same as Case 13
15	Viridans Streptococcus, moderate numbers	Staphylococcus aureus A, many	None	Same as Case 13
16	K. pneumoniae, many	Hemolytic Streptococcus, moderate; Staphylococcus aureus A, moderate numbers	Occasional micro-organisms in surface exudate; very few within tissue	Same as Case 13

Gram-positive cocci were localized in an area of superficial necrosis, with a few micro-organisms scattered just beneath the basement membrane. In Case 8 there were also a few scattered cocci beneath the basement membrane.

The second group of eight cases were patients with intrinsic asthma from whom antral membrane was obtained by trephine through the inferior meatus (Table 7). In two cases cultures of membrane biopsy were sterile, as were pretrephine irrigations. In two others nonpathogens only were obtained, although in one of these pretrephine irrigation yielded many colonies of B. proteus. Micropathology of all four of these specimens again showed a typical allergic reaction, and in none were micro-organisms seen on section.

The four remaining biopsy specimens did not show an allergic tissue reaction. They showed acute and chronic nonspecific inflammation characterized by infiltration with neutrophiles, lymphocytes, and plasma cells in a denser stroma. Case 13 yielded many colonies of S. aureus A, although irrigations had been sterile. In Case 14 both membrane and irrigation showed B. proteus in many colonies. Case 15 yielded moderate numbers of viridans Streptococcus on irrigation and many colonies of S. aureus A from membrane. Case 8 grew K. pneumoniae from irrigations and hemolytic streptococci and S. aureus A in moderate numbers from the membrane. One of these membranes showed occasional micro-organisms in surface exudate and very few within tissue.

Seven of the membranes with the histopathologic changes characteristic of allergy either were sterile or yielded only nonpathogens. In none of these were micro-organisms seen on sections. In two allergic membranes micro-organisms were seen situated superficially and in small numbers. Four membranes did not show an allergic reaction but showed the common nonspecific alterations associated with reaction to infection, and from these pathogens or potential pathogens in appreciable numbers were recovered.

TABLE 8.—*Provocative Tests with Autogenous Sinus Vaccines in Bronchial Asthma*

		Asthma Responses					
		Diluted Vaccine*		Full-Strength Vaccine†			
Case	Micro-Organisms	0.1 Ml.	0.5 Ml.	0.1 Ml.	0.3 Ml.	0.5 Ml.	1.0 Ml.
1	Pneumococcus, Type 25 (membrane)	.....	Neg.	Neg.	.....	Neg.	.....
2	K. pneumoniae	Pos. / Pos.	.....	Neg.	.....	Neg.	.....
3	Hemolytic Strep. (membrane)	Neg.	.....	Pos. / Neg.	Neg.	Neg.	.....
	Staphylococcus aureus A	.....	.....	Neg.	Neg.	Neg.	.....
4	Staphylococcus aureus A	Pos. / Neg.	.....	Pos.	Pos. / Neg.	Neg.	Neg.
5	Staphylococcus aureus A	Pos. / Neg.	.....	Pos.	.....	Neg.	.....
6	Staphylococcus aureus A	.....	.....	.....	.....	Neg.	Pos. / Neg.

* 100,000,000 organisms per milliliter.
† 1,000,000,000 organisms per milliliter.

5. Asthma Responses to Provocative Injections of Autogenous Sinus Vaccines

The symptomatic asthma response to the injection of an autogenous sinus vaccine has been offered as evidence of the specific etiologic relationship of sinus micro-organisms to bronchial asthma. In this study 11 patients with intrinsic asthma were given 45 trial subcutaneous injections of 12 autogenous vaccines. The micro-organisms were obtained chiefly from cultures of sinus irrigations and in two instances from sinus mem-

TABLE 9.—*Provocative Tests with Autogenous Sinus Vaccines in Bronchial Asthma*

		Asthma Responses					
		Diluted Vaccine*		Full-Strength Vaccine†			
Case	Micro-Organisms	0.1 Ml.	0.5 Ml.	0.1 Ml.	0.3 Ml.	0.5 Ml.	1.0 Ml.
7	Pneumococcus, Type 15	Neg.	Neg.	Neg.	.....	.....	Neg.
8	Staphylococcus aureus A	.....	Neg.	.....	Neg.	.....	Pos.
9	Staphylococcus aureus A			Neg.	.....	Neg.	Neg.
10	Pneumococcus, Type 1	.....	.....	Pos. / Neg.	.....	Neg.	.....
11	Pneumococcus, Type 23	.....	.....	Neg.	.....	Neg.	Neg.

* 100,000,000 organisms per milliliter.
† 1,000,000,000 organisms per milliliter.

brane. Initial injections were usually of vaccine diluted 1 : 10, but in all cases rapidly increased doses of full-strength vaccine, 1,000,000,000 micro-organisms per milliliter, were administered (Tables 8 and 9).

In five cases no asthma responses were elicited after 16 trial injections. Four patients reacted with asthma once after injection but gave negative responses on two to four additional test doses each. In Cases 2, 4, and 5, one gave three positive asthma responses and two gave two positive reactions. Each of these patients also gave negative responses on two to four other trials, even when larger doses of vaccine were given. In all, there were 11 positive responses among 45 trial injections.

This small series of observations suggests that single positive asthma responses after injections of vaccines must be interpreted with caution. If the symptomatic asthma reaction cannot be consistently reproduced, it appears doubtful that it should be interpreted as a specific response to the vaccine, indicative of bacterial allergy.

6. Follow-Up Study of Sinus Surgery in Asthma

Sixty-one cases of asthma, presumed to be associated with infectious sinus disease, had follow-up observations from 1 to 14 years after sinus surgery. These cases were divided into two groups. The first, a group of 31 cases, had sphenoethmoidal and radical antral surgery, including Caldwell-Luc or crestectomy procedures (Table 10). The second group, of 30 cases, had sphenoethmoidal surgery with simple intranasal antrotomies instead of radical antrum procedures (Table 11).

The results in the first group were as follows: Six were found to have had a distinctly more favorable course after operation. Of these, two experienced prolonged arrest or "cure" of the asthma. Twenty-five were unimproved or worse.

The postoperative rhinologic status was evaluated in 28 of the 31 cases. Polypoid regrowth was present in 12 cases, and gross sinus infection, in 7. Nine cases manifested no evidence of recurrent polypoid disease or infection. Thus the final rhinologic result

TABLE 10.—*Follow-Up Study of Sinus Surgery in Bronchial Asthma: 1. Radical Antrum Operation*

		Asthma			Rhinologic Status		
Follow-Up, Yr.	Cases, No.	Unimproved or Worse	Prolonged Improvement	Remission ("Cure")	Polypoid Regrowth	Reinfection	Clear
1-3	13	11	2	0	2	2	5
4-7	9	6	1	2	5	2	1
8-11	5	5	0	0	2	1	2
12-14	4	3	1	0	3	2	1
Totals	31	25	4	2	12	7	9

was unsatisfactory in the majority of our cases, despite repeated surgical procedures and careful postoperative care.

Of interest, too, was the often paradoxical relationship between the rhinologic status and the effect upon the asthma following radical sinus surgery. Three of the six cases with clinical improvement of the asthma, including both cases of "cure," showed evidence of return of polypoid disease. On the other hand, among the nine cases with good postoperative rhinologic results only one was observed to have experienced any significant improvement of the asthma following the operative procedures.

The results in the second follow-up group, without radical antrum surgery, were as follows: Thirteen patients had a more favorable course after operation. Of these, four experienced a prolonged remission or "cure" of the asthma. Seventeen were unimproved or worse.

TABLE 11.—*Follow-Up Study of Sinus Surgery in Bronchial Asthma: 2. No Radical Antrum Operation*

		Asthma			Rhinologic Status		
Follow-Up, Yr.	Cases, No.	Unimproved or Worse	Prolonged Improvement	Remission ("Cure")	Polypoid Regrowth	Reinfection	Clear
1	4	3	0	1	0	0	4
2-3	12	5	4	3	3	2	5
4-5	6	2	4	0	2	0	3
6-7	8	7	1	0	3	1	4
Totals	30	17	9	4	8	3	16

The postoperative rhinologic status was evaluated in 27 of the 30 cases. Polypoid regrowth was present in eight cases and gross sinus infection in three. Sixteen cases manifested no evidence of recurrent ethmoidal polypoid disease or infection.

Comparison of the results of the two follow-up groups shows a greater frequency of improvement in the asthma in patients who did not have radical antral surgery. While it is probable that the severity of the asthma may not have been the same in the two groups of cases, the data do illustrate that improvement of asthma and even apparent "cure" may occur without complete removal of presumed bacterial foci. A favorable course was observed in a minority of the cases in both groups following operation.

COMMENT

Our findings in this study emphasize the need for more precise criteria in the diagnosis of sinus disease as a focus of infection. Particularly in vasomotor or allergic patients, the careful differentiation between infected secretion and membrane and vasomotor secretion and membrane is of vital importance if proper therapy is to be employed.

For over 20 years the relationship of sinus infection to the underlying pathologic alterations of the mucous membrane and to the accompanying asthma has been a matter of controversy. On the one hand there has been the point of view that the sinus infection is the sole primary cause for the membrane changes and asthma, mediated through a mechanism of bacterial allergy.§ The edematous, eosinophile-infiltrated sinus membrane with micro-organisms described as uniformly present deep in the tissues is considered objective proof of bacterial allergy. Opposed to this has been the viewpoint that sinus infection is most often secondary and superimposed upon an already abnormal allergic or vasomotor membrane. Those who hold this opinion have not regarded infection as a frequent cause either of the membrane pathology or of the accompanying asthma, although the infection may affect the course of both.‖

We have submitted the following observations, which we believe support the latter

§ References 4-6.

‖ References 7 and 8.

concept: (1) the absence of demonstrable infection as judged by our criteria in many cases with sinus membrane alterations; (2) the lack of consistent correlation between roentgen and bacteriologic findings of the sinuses; (3) no proof of sinus infection in many cases of intrinsic asthma; (4) the long-term bacteriologic data which indicate the occurrence of transient and multiple infections of the sinuses in asthma, thus suggesting the probability of superimposed infection; (5) the preponderance of negative asthma responses to multiple provocative injection of autogenous sinus vaccines, and (6) the finding that sinus membranes may show typical allergic pathologic alterations despite the absence of significant micro-organisms on culture or in sections.

Extensive membrane disease affecting all sinuses was commoner in the intrinsic than in the extrinsic asthma group, as has been previously reported by Weille.[7] This may account for the greater frequency of infection in the intrinsic cases, as emphasized by proponents of the bacterial allergy theory. Severe asthmatic reactions may follow upon injections of tuberculin.[10] Such reactions after injections of upper respiratory vaccines may likewise be nonspecific in character.

At this point we should like to indicate our acceptance of the general bacterial allergy hypothesis as illustrated by the initiation of a systemic disease by an upper respiratory infection. The classical example of this is probably the relationship of acute hemolytic streptococcal infection of the pharynx to rheumatic fever. In the course of this study, for instance, we have seen paranasal sinus infections precipitate the development of erythema nodosum and periarteritis nodosa. In children, particularly, the sequence of asthma following acute upper respiratory infections is common, although the precise mechanism remains obscure. However, in such instances, as in the cases of our own series with multiple sinus pathogens, one must envision so broad a spectrum of bacterial and/or viral reactivity as to raise the question whether such a reaction could be one of specific allergy.

There is a difference of opinion concerning the effectiveness of radical sinus surgery in bronchial asthma.¶ In our small series, improvement of asthma was twice as frequent when surgery did not include removal of antral membrane. The severity of asthma in the two patient groups may not have been comparable, and so no conclusion is offered as regards the superiority of one type of surgery over the other. However, the results are of interest in that improvement of asthma, even apparent arrest of the disease, occurred without eradication of the presumed focus of bacterial allergy.

The data gathered, we believe, also add support to the view that the therapeutic approach to sinus disease in asthma should be conservative. The extent of treatment should be determined by the local findings rather than by the concept of bacterial allergy. The use of sinus irrigations in conjunction with antibiotic therapy, systemically and locally, is the initial treatment of choice. When postnasal discharge, even of noninfected secretion, aggravates cough or asthma, or noninfected polypoid sinus disease causes obstruction, conservative surgery may be required. Only when there is evidence of persistent infection associated either with local symptoms or with intractable asthma do we feel justified in contemplating the use of radical sinus surgery.

SUMMARY AND CONCLUSIONS

Eighty-two patients with bronchial asthma had complete sinus investigations to determine the role of sinus infection in their disease. The study included allergic, rhinologic, and sinus x-ray examinations together with microscopic and bacteriologic studies of nasal and sinus secretions. Precise criteria of infection were emphasized.

Among 58 cases of intrinsic asthma, 25 had sinus infection and 33 were free from infection. Among 24 extrinsic cases 5 had sinus infection and 19 were free from infection. Although sinus infection was more frequent in the intrinsic group, it was present

¶ References 10-13.

in less than half of such cases in which infection is usually considered as a causative factor.

Bacteriologic observations of sinus secretion made repeatedly, in some cases over many months, revealed the occurrence of transient and multiple infections. These findings suggest that the micro-organisms isolated cause infection on a previously abnormal membrane as a result of vasomotor or allergic influences rather than act as etiologic agents responsible for the alterations in the sinus membrane.

In the correlation of sinus roentgenograms with bacteriologic findings, of 42 cases with positive x-rays 24 showed sinus infection while 18 were free from infection. Of 29 cases with negative x-rays, 9 showed sinus infection while 20 were free from infection. Although sinus infection was more frequently associated with abnormal sinus membrane, such membrane disease may occur without infection and infection may occur without membrane disease in asthmatic patients.

Bacteriologic and micropathologic study of antral membrane was done in 16 cases of intrinsic asthma. In seven cases membranes showed an allergic reaction with many eosinophiles, edema, and thickening of basement membrane, although cultures yielded no growth or only nonpathogens. None of these showed micro-organisms on tissue sections. Four membranes with the same pathology had small to moderate numbers of potential pathogens in cultures. On tissue sections micro-organisms were seen localized near the surface in one membrane. Pathogens were obtained from a single allergic membrane, and a few micro-organisms were seen beneath the basement membrane. Four membranes showed nonspecific acute and chronic inflammation and yielded pathogens. In one of these membranes micro-organisms were visible on section but were located superficially.

Bacteriologic and micropathologic study of antral membranes indicates that hyperplastic allergic tissue alterations may occur in the absence of infection. Sinus infection when present appears to be located chiefly near the surface of the membrane.

Multiple subcutaneous provocative injections of 12 autogenous sinus vaccines were administered to 11 patients with intrinsic asthma. There were 11 positive and 34 negative asthma responses among 45 trial injections. Single positive asthmatic reactions to vaccines should not be interpreted as signifying specific bacterial allergy.

A follow-up study of 1 to 14 years after sinus surgery in 61 asthmatics deals with two groups of cases, with and without radical antrum operation. Definite improvement in asthma occurred twice as often in the group without removal of antral membrane, although only a minority of patients were benefited in either group. Arrest of asthma may occur even though antral membrane is not removed. Significant improvement of asthma after radical sinus surgery may occur despite the regrowth of polypoid tissue, and, paradoxically, there may be no improvement of asthma despite an excellent postoperative rhinologic status.

The findings offered in this study appear to warrant the conclusion that sinus infection, as a rule, is not a primary cause of asthma but rather a complication superimposed on altered sinus membrane.

The management of sinus disease should include at first conservative measures and later such surgery as dictated by local nasosinal abnormalities and by persistent infection. The decision to employ radical sinus procedures should be determined by these factors rather than by the concept of bacterial allergy alone.

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Optimal Effective Dose of Anticholinergic Drug in Peptic Ulcer Therapy

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In our previous study [1] on the effect of different doses of an anticholinergic drug in the same patient, we found that suppression of gastric acidity to pH 4.5 or higher did not occur at any dose without accompanying dryness of the mouth but that the dose producing dryness of the mouth did not necessarily bring about such pH values of acidity. However, if the dose of these drugs was increased to one increment below that which produced uncomfortable symptoms of parasympathetic inhibition, such as blurring of vision, palpitation, dizziness, headache, weakness, flushing of the face, and/or excessive dryness of the mouth and throat, suppression of acidity to pH 4.5 or higher occurred consistently with the effective drugs. This dose we termed the optimal effective dose (O. E. D.).

The present study was undertaken to investigate the value of the optimal effective dose of anticholinergic drugs and to appraise its usefulness in the treatment of peptic ulcer. Studies were carried out to determine the effect of a single O. E. D. of tricyclamol (Elorine) methylsulfate (1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulfate), mepiperphenidol (Darstine) bromide, propantheline (Pro-Banthine) bromide, and belladonna tincture on basal gastric secretion. Basal secretion was also studied the day after continued oral intake of the O. E. D. of Elorine sulfate.

In order to appraise the possible usefulness of the O. E. D. of an anticholinergic drug in the treatment of peptic ulcer, comparative studies were done on the pH of the gastric contents hourly, day and night. The effect of a single "recommended" dose or O. E. D. of tricyclamol methylsulfate on gastric secretion induced by emotional stress and by insulin hypoglycemia was also investigated.

METHOD OF STUDY

In this study the O. E. D. was determined as follows: on the first day, the "recommended" (commercial) dose of the drug was administered three times daily, before each meal, and at bedtime, then increased by one increment daily until any of the uncomfortable symptoms of parasympathetic inhibition noted above occurred. Then the dose of drug was decreased by one increment daily till uncomfortable symptoms disappeared. This dose constituted the O. E. D. for the patient. The following dosage increments were used: tricyclamol methylsulfate, 50 mg.; mepiperphenidol bromide, 50 mg.; propantheline bromide, 15 mg., and belladonna tincture, 2 drops (0.12 cc.).

The investigations were divided into four categories:

1. The effect of a single O. E. D. of tricyclamol methylsulfate, mepiperphenidol bromide, propantheline bromide, and belladonna tincture upon basal gastric secretion was determined in 46 experiments, performed in 22 patients with chronic duodenal ulcer secreting acid gastric juice continuously. The drug was given intraduodenally, and details of the technique employed have been described previously.[1]

2. The effect of continued oral administration of the O. E. D. of tricyclamol methylsulfate upon basal gastric secretion was investigated in seven patients with chronic duodenal ulcer. One hour's basal gastric secretion was collected during a control period.

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On the day following, a 14-day period of continued oral administration, four times a day, of the O. E. D. of tricyclamol methylsulfate was begun, following which another one hour's basal secretion was collected. Five of the seven patients received in addition an O. E. D. at 3:30 a. m. on the morning of the test. A second control period of one hour's basal gastric secretion was collected a week later, during which interval no drug had been administered.

3. Comparative studies were done on the pH of the gastric contents hourly throughout the day and night with milk and cream mixture alone and successively in addition with the "recommended" dose or the O. E. D. of tricyclamol methylsulfate or a mixture of aluminum hydroxide and magnesium trisilicate (AMT), singly or in combination, in eight patients with chronic duodenal ulcer. Similar studies were done with mepiperphenidol bromide. All patients were hospitalized. After a 14-hour fasting period, a 14 F. Levin tube was introduced under fluoroscopic observation through the nose into the stomach so that the tip of the tube rested in the gastric antrum. Aliquots of 5 cc. of the gastric contents were taken at hourly intervals throughout the day and night. The specimens were drawn before each feeding and filtered, and the pH was determined with a Beckman pH meter. In each patient the following schedules were employed on different days:

Schedule A: Milk and cream mixture (7 oz. [210 cc.] of milk, 1 oz. [30 cc.] of light cream, and 1 tablespoonful [15 cc.] of skim milk powder), given orally, every hour on the hour, from 8:00 a. m. to 11:00 p. m.

Schedule B: Schedule A plus the "recommended" dose (50 mg.) of tricyclamol methylsulfate orally, at 8:00 a. m., 1:00 p. m., 6:00 p. m., 11:00 p. m., and 3:30 a. m.

Schedule C: Schedule A plus the O. E. D. of tricyclamol methylsulfate orally, given at the same time intervals as in Schedule B.

Schedule D: Schedule A plus 15 cc. of AMT, given orally, every two hours, from 8:00 a. m. to 12 midnight.

Schedule E: Schedule D plus the O. E. D. of tricyclamol methylsulfate given at the same time intervals as described under Schedule B.

Schedule F: the same as Schedule C, except that the 3:30 a. m. O. E. D. of tricyclamol methylsulfate was omitted.

4. Studies were done on the effect of a single "recommended" dose (50 mg.) and the O. E. D. of tricyclamol methylsulfate on gastric secretion induced by emotional stress and by insulin hypoglycemia. Detailed techniques of these studies will be presented elsewhere, and only preliminary findings will be discussed here.

We selected the duration of suppression of gastric acidity to pH 4.5 or higher as the main criterion for judging significant antisecretory potency, since the intent in reducing acidity in the ulcer patient actually is to reduce peptic activity. At pH 4.5, peptic activity is almost zero.[2]

TABLE 1.—*Mean Volume, Free Acid Output, Total Acid Output, and Pepsin Output for Control and After Intraduodenal Administration of a Single O. E. D. of the Anticholinergic Drug*

Drug	Cases, No.	Time Lapse After Administration of Drug, Hr. 0	1	2	3	4
Mean volume, ml.						
Isotonic sodium chloride solution	22	95.6	90.6	86.8	85.1	93.9
Mepiperphenidol bromide	13	92.7	36.5	27.5	29.8	52.7
Tricyclamol methylsulfate	16	94.7	35.8	16.9	10.9	16.1
Propantheline bromide	12	99.6	25.7	16.4	16.4	28.4
Belladonna tincture	5	75.8	49.5	40.0	53.8	45.7
Mean free acid output, mEq.						
Isotonic sodium chloride solution	22	4.32	4.19	4.17	3.68	4.34
Mepiperphenidol bromide	13	4.23	0.48	0.15	0.35	1.58
Tricyclamol methylsulfate	16	4.59	0.61	0.05	0.01	0.14
Propantheline bromide	12	5.14	0.46	0.11	0.08	0.52
Belladonna tincture	5	4.31	2.34	1.85	2.72	2.34
Mean total acid output, mEq.						
Isotonic sodium chloride solution	22	5.85	5.50	5.48	5.01	5.92
Mepiperphenidol bromide	13	5.87	1.10	0.52	0.79	2.40
Tricyclamol methylsulfate	16	6.36	1.16	0.33	0.16	0.41
Propantheline bromide	12	6.75	0.83	0.36	0.32	0.96
Belladonna tincture	5	5.86	3.48	2.71	3.90	3.27
Mean pepsin output, Mett units						
Isotonic sodium chloride solution	22	18866	21863	19494	19060	21591
Mepiperphenidol bromide	13	19385	5134	4477	8705	8259
Tricyclamol methylsulfate	16	15514	3613	1344	1236	2788
Propantheline bromide	12	19813	3314	2217	2316	5398
Belladonna tincture	5	8656	7049	3889	7845	5869

TABLE 2.—*Duration of Suppression of Acidity of the Level of pH 4.5 or Higher After Intraduodenal Administration of a Single O. E. D. of the Anticholinergic Drug*

Case	Age, Yr.	Sex	Tricyclamol Methylsulfate			Mepiperphenidol (Darstine) Bromide			Propantheline (Probanthine) Bromide			Belladonna Tincture	
			Dosage		Duration pH >4.5, Min.	Dosage		Duration pH >4.5, Min.	Dosage		Duration pH >4.5, Min.	Dose, Drops	Duration pH >4.5, Min.
			Mg.	Mg./Kg.		Mg.	Mg./Kg.		Mg.	Mg./Kg.			
1	18	F	250	2.96	90	400	4.74	60	105	1.25	60	35	0
2	32	F	150	3.12	>270	50	1.04	90	30	0.63	45	32	0
3	46	F	150	1.50	>180	300	3.00	180	120	1.20	>240	24	0
4	25	F	200	3.33	>240	100	1.67	>240	75	1.25	>240	22	225
5	34	M	200	3.28	>240	250	4.10	195	90	1.47	180	26	180
6	39	M	200	3.64	60	300	5.45	165	120	2.18	90	..	..
7	25	M	350	3.99	>240	350	3.99	>240	...	....	..	..	..
8	41	M	150	2.27	>240	...	....	..	75	1.14	165	..	..
9	41	M	350	6.36	30	...	....	..	120	2.18	0	..	..
10	23	M	400	5.86	150	...	....	..	75	1.10	>180	..	..
11	54	F	250	2.78	>180	...	....	..	...	....	..	..	..
12	44	M	200	2.93	105	...	....	..	...	....	..	..	..
13	41	M	150	1.94	105	...	....	..	...	....	..	..	..
14	51	M	500	9.01	180	...	....	..	...	....	..	..	..
15	74	M	200	3.33	>180	...	....	..	...	....	..	..	..
16	56	M	350	5.43	75	...	....	..	...	....	..	..	..
17	40	F	...	....	..	150	2.73	60	30	0.54	105	..	..
18	19	M	...	....	..	400	5.00	45	105	1.31	30	..	..
19	41	M	...	....	..	150	2.66	60	30	0.53	60	..	..
20	39	M	...	....	..	300	3.57	165	...	....	..	..	..
21	28	M	...	....	..	50	1.11	45	...	....	..	..	..
22	30	M	...	....	..	250	4.17	75	...	....	..	..	..

Side-effects were evaluated in patients on prolonged administration of the drug. The clinical safety of these drugs was investigated by frequent complete blood cell counts, differential blood smears, and urine analysis. Blood urea nitrogen determination, renal phenolsulfonphthalein-excretion test, and hepatic function tests were done at intervals.

RESULTS

Effect of a Single Optimal Effective Dose (O. E. D.)

Analysis of the data in Table 1 shows that the intraduodenal administration of a single O. E. D. of tricyclamol methylsufate, mepiperphenidol bromide, or propantheline bromide produced a pronounced and significant decrease in volume and in free and total acid output, as well as in output of pepsin, of the gastric juice. The inhibitory effect continued for more than four hours. Belladonna tincture had relatively moderate activity over the four-hour period.

Table 2 shows the optimal effective dose, dose per kilogram body weight, and duration of suppression of gastric acidity to pH 4.5 or higher after the intraduodenal administration of a single O. E. D. of drug. In five patients, all the drugs were studied on different days; in others, only one, two, or three drugs were evaluated in the same person. Tricyclamol methylsulfate was effective, in that it produced suppression of gastric acidity to pH 4.5 or higher in all 16 patients examined. The duration of this suppression continued for 30 minutes to more than 270 minutes, and in 9 of the 16 suppression lasted longer than 3 hours. Significantly, the O. E. D. for tricyclamol methylsulfate varied from 150 mg. in one patient to 500 mg. in another; and, calculated in terms of milligrams per kilogram body weight, represented doses from 1.50 to 9.01 mg./kg. Similarly, mepiperphenidol bromide was effective in all of 13 subjects, and the O. E. D. ranged from 50 to 400 mg., or 1.04 to 5.45 mg./kg. body weight. Propantheline bromide was effective in 11 of the 12 patients tested, and the O. E. D. varied from 30 to 120 mg., or 0.53 to 2.18 mg./kg. body weight. A person requiring a higher dose of one effective drug need not necessarily require the same relatively high dose of another. Belladonna tincture, on the other hand, was effective in only two of five patients, and the O. E. D. ranged from 22 to 35 drops (0.66 to 2.1 cc.). The three patients whose gastric contents failed to show any period of pH 4.5 or higher after belladonna tincture did respond to tricyclamol methylsulfate, mepiperphenidol bromide, and propantheline bromide.

Basal Gastric Secretion Following Continued Oral Administration of Tricyclamol Methylsulfate

Figure 1 presents the volume, total acid output, and duration of pH 4.5 or higher

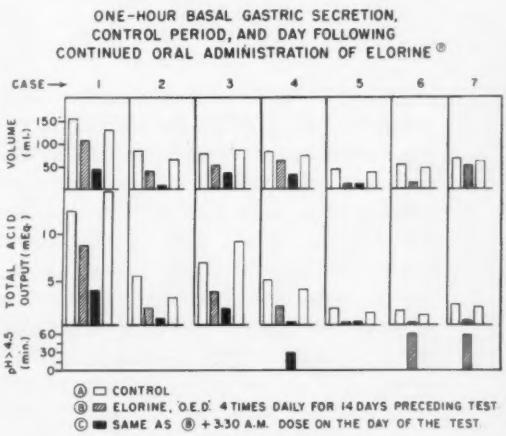
ONE-HOUR BASAL GASTRIC SECRETION, CONTROL PERIOD, AND DAY FOLLOWING CONTINUED ORAL ADMINISTRATION OF ELORINE®
CASE→ 1 2 3 4 5 6 7
VOLUME (ml.)
150
100
50
TOTAL ACID OUTPUT (mEq.)
10
5
pH>4.5 (min.)
60
30
0
Ⓐ CONTROL
Ⓑ ELORINE, O.E.D. 4 TIMES DAILY FOR 14 DAYS PRECEDING TEST
Ⓒ SAME AS Ⓑ + 3.30 A.M. DOSE ON THE DAY OF THE TEST

Fig. 1.—One-hour basal gastric secretion, control period, and day following continued oral administration of tricyclamol (Elorine) methylsulfate.

of the gastric juice for each control period and for the day following continued oral administration of O. E. D. of tricyclamol methylsulfate. A reduction in volume and in free and total acid output of the basal gastric secretion occurred the day after administration of the drug. The mean hourly volume was 57.7% of that of the control period; the mean hourly free acid output, 28.1%, and the mean hourly total acid output, 21.9%. In two of the seven patients the suppression of gastric acidity produced a pH 4.5 or higher. In the other five, who received an

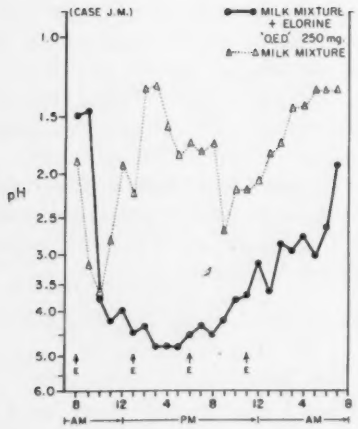

Fig. 2.—Hourly pH of the gastric contents, day and night, in patient J. M., after milk mixture alone (Schedule A) and plus O. E. D. of tricyclamol methylsulfate (Schedule F).

additional O. E. D. of tricyclamol methylsulfate at 3:30 a. m. on the morning of the test, further reduction in volume and in free and total acid output of gastric secretion followed. The mean hourly volume on this schedule was 31.9% that of the control period; the mean free acid output, 11.9%, and the mean total acid output, 19.8%. One of these five patients showed a suppression of gastric acidity that resulted in pH 4.5 or higher.

Hourly pH of the Gastric Contents Day and Night

The results yielded the following general patterns:

Figure 2 depicts the results in Patient J. M. The dotted line and open triangles represent the pH of the gastric contents throughout the day and night after oral administration of the milk mixture (Schedule A), whose pH measured 6.55. The action of this mixture we considered ineffective, in that all the pH values were below 4.5. The solid line and closed circles illustrate the results after the milk mixture plus O. E. D. of tricyclamol methylsulfate (Schedule F). The O. E. D. for this patient was 250 mg. This schedule was partially effective, in that a significant reduction in acidity of the gastric contents occurred, producing pH values 4.5 or higher for a period of 6 hours and pH 3.5 or higher for 14 hours. During the night, pH values gradually decreased and free hydrochloric acid appeared in the gastric contents. These results prompted the administration of an additional dose of tricyclamol methylsulfate at 3:30 a. m. in an attempt to control the night secretion.

Figure 3 shows the results in Patient B. S. The dotted line and open triangles again represent the pH of the gastric contents after the milk mixture (Schedule A); and the broken line and open circles, after milk mixture plus the "recommended" dose (50 mg.) of tricyclamol methylsulfate (Schedule B). Both were ineffective, since all pH values were under 4.5. The broken line and crosses represent the results after the milk mixture plus AMT (Schedule D). The pH of the AMT was 7.28. This combination was partially effective, in that free

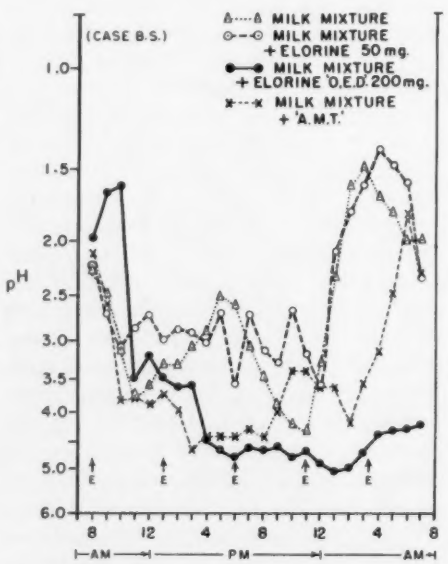

Fig. 3.—Hourly pH of the gastric contents, day and night, in patient B. S., after milk mixture alone (Schedule A) and plus the "recommended" dose (Schedule B) or the O. E. D. (Schedule C) of tricyclamol methylsulfate or AMT (Schedule D).

hydrochloric acid was absent for seven hours, but only one specimen attained a pH value above 4.5. During the night, pH values gradually decreased and free hydrochloric acid appeared in the gastric contents. The solid line and closed circles represent the results after the milk mixture plus the O. E. D. of tricyclamol methylsulfate (Schedule C). The O. E. D. for this patient was 200 mg. This schedule produced pH values of 4.5 or higher for 12 hours (4:00 p. m. to 3:00 a. m.), and even after 3:00 a. m.

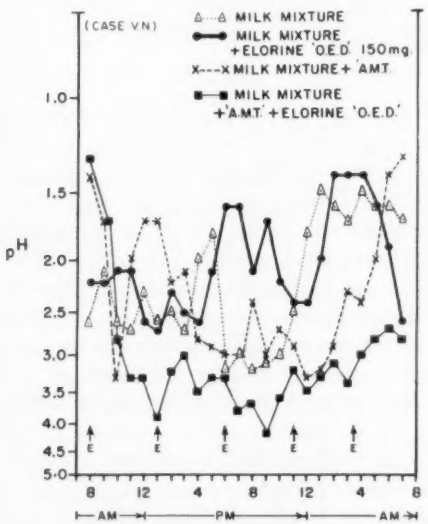

Fig. 4.—Hourly pH of the gastric contents, day and night, in patient V. N., after milk mixture alone (Schedule A) and plus the O. E. D. of tricyclamol methylsulfate (Schedule C) or AMT (Schedule D) or their combination (Schedule E).

they were 4.0 or greater. The results of the combined use of milk mixture, AMT, and O. E. D. of tricyclamol methylsulfate (Schedule E) in this patient were no better than those obtained with the milk mixture and O. E. D. of tricyclamol methylsulfate (Schedule C). This result was observed in four of the eight patients.

The type of response in the other four patients studied is illustrated in Figure 4, in Patient V. N. The dotted line and open triangles represent the pH of the gastric contents after the milk mixture (Schedule A). This was ineffective. The addition of the O. E. D. of tricyclamol methylsulfate to the milk mixture (Schedule C) also failed to control adequately the pH of the gastric contents, represented by the solid line and closed circles. The O. E. D. for this patient was 150 mg. The "recommended" dose (50 mg.) of tricyclamol methylsulfate (Schedule B) was also ineffective. The broken line and crosses represent the results after the milk mixture plus AMT (Schedule D). All pH values were less than 3.5, and free hydrochloric acid was present in all specimens. The solid line and closed squares show the results after the combined administration of the milk mixture, AMT, and the O. E. D. of tricyclamol methylsulfate (Schedule E). There was a significant reduction in the acidity of the gastric contents, with pH values maintained at higher values than in any of the other four studies. Similar types of response were obtained with mepiperphenidol bromide.

Effect of Tricyclamol Methylsulfate on Gastric Secretion Induced by Emotional Stress and by Insulin Hypoglycemia

Figure 5 shows the results in Patient E. M. The dotted line and open triangles represent the basal gastric secretion in this patient over a six-hour period. Each dot represents a 15-minute total acid output, expressed in per cent of the mean of the four 15-minute specimens of the first hour's basal secretion. The solid line and closed circles illustrate the response to emotional stress. One hour's basal secretion was collected; a disturbing interview by the psychiatrist, indicated by an arrow, lasting approximately 30 minutes and based on the patient's conflicts determined in previous interviews, was then carried out. This produced an initial depression of gastric secretion, which was followed by an increase with the peaks in the third and fourth hours at 700% of the mean basal secretion. These peaks correspond to what we have reported as the late phase of gastric secretory response to insulin

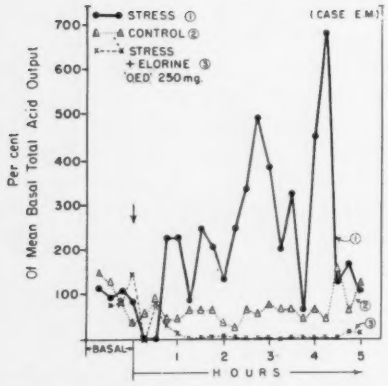

Fig. 5.—Curves of total acid output, expressed in per cent of the mean 15-minute output of the first-hour basal secretion. Control basal secretion and secretion after emotional stress and after emotional stress plus O. E. D. of tricyclamol methylsulfate intraduodenally.

hypoglycemia and have shown in man to represent the adrenal phase of gastric secretion,[3] * as did Porter and his associates in the monkey.† The smaller peaks in the first two hours, lesser vagal effects, probably represent the effects of anterior hypothalamic stimulation. The broken line and crosses illustrate the results under emotional stress and, in addition, a single O. E. D. of tricyclamol methylsulfate intraduodenally. This was administered just before the interview by the psychiatrist. The O. E. D. for this patient was 250 mg. It inhibited gastric secretion throughout the four-hour period following the interview.

In Figure 6, the solid line and closed circles represent the pH values of the gastric secretion under emotional stress plus a single "recommended" dose (50 mg.) of tricyclamol methylsulfate. The broken line and crosses show similar results under emotional stress plus O. E. D. of tricyclamol methylsulfate. The latter dose produced a pronounced inhibition of "stress" gastric secretion, with pH values above 4.5 for four hours; while the single "recommended" dose produced similar depression for only one hour. Repeat studies were done under control conditions and emotional stress in this same patient, with similar results. These will be published in detail separately.

Preliminary data of the effect of tricyclamol methylsulfate on the gastric secretion induced by insulin hypoglycemia show that an O. E. D. can produce partial inhibition of the early phase (vagal) of the gastric secretion and a pronounced inhibition of the late phase (adrenal) in some persons.

COMMENT

Of all the factors that have been suggested as contributory to the development of peptic ulcer, that of acid-pepsin has long been considered a *sine qua non*. If optimum conditions for the healing of an ulcer are to be achieved, peptic activity must be inhibited. Since no practicable methods for either inhibiting the secretion of pepsin or inactivating the enzyme in the ulcer patient are available, neutralization or inhibition of acid secretion to a point where peptic activity

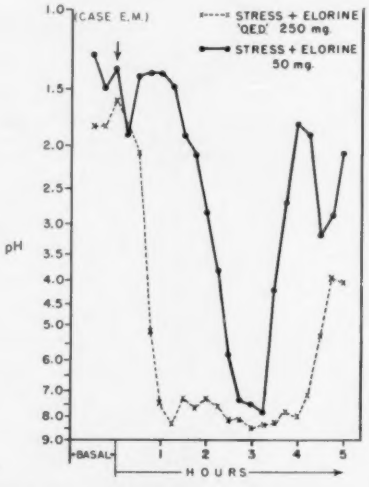

Fig. 6.—pH values of the gastric contents during emotional stress plus one "recommended" dose (50 mg.) and emotional stress plus one O. E. D. (250 mg.) of tricyclamol methylsulfate.

* More recent experimental evidence obtained in persons with vagotomy only suggests that the maximal response of the adrenal phase of gastric secretion is dependent upon an intact vagal mechanism.

† References 4 and 5.

no longer occurs currently offers the sole approach to the problem. Such inhibition could be possible if the pH of the gastric contents could be maintained continuously at pH 4.5 or higher; for at pH 4.5 peptic activity is reduced almost to zero. The internist tries to accomplish this result through the use of various drugs that either neutralize acid or inhibit its secretion; the surgeon by vagotomy and/or subtotal gastrectomy attempts to reduce the output of acid and pepsin.

An effort to estimate critically the efficiency of drug therapy in patients with duodenal ulcer is beset by many pitfalls. An evaluation based on relief of symptoms involves the drawbacks inherent in any subjective analysis and an inability to exclude the many factors that must influence the course of the disease. The rate of healing of the ulcer crater measured roentgenographically is objective enough, but the exact relation of the size of the crater to the rate of healing is by no means yet fully established and the roentgen disappearance of an ulcer crater does not supply unequivocal evidence of complete healing. Although the rate of recurrence of ulcers could offer a reasonable measure of the efficacy of a therapeutic program, it involves too long a term of study to be practical, especially if a number of new agents are to be evaluated. An immediate appraisal of the effectiveness of any new drug could be achieved objectively by a study of its effect on the gastric secretory response in patients with peptic ulcer if a drug alone or in proper combination with other measures could be shown consistently and effectively to produce and maintain a pH of the gastric contents of 4.5 or higher throughout the 24-hour period. With such a result, eventual complete healing of the ulcer could be anticipated. The anticholinergic drugs are currently receiving the greatest attention in the treatment of ulcers, since they appear to be the most promising pharmacologic agents available at present for producing inhibition of gastric secretion. From the clinical standpoint, the ideal anticholinergic drug should consistently inhibit the output of hydrochloric acid so as to maintain a pH of the gastric contents that inhibits peptic activity for long periods after its oral ingestion, should produce no or only minimal side-effects, should be free of inducing tolerance, and should be inexpensive.

In recent years many anticholinergic drugs have appeared on the market with literature to support claims for their acid antisecretory action in man. Yet one must be impressed with the conflicting results obtained by different investigators. In these reports, a comparison of antisecretory potency of various compounds has been made from the action of doses of the drug selected either on a body weight basis or on dosages recommended by the pharmaceutical company.

In our study, we found that none of the anticholinergic drugs produced suppression of gastric acidity to pH 4.5 or higher without accompanying dryness of the mouth and that the degree of dryness was not constant on a given dose in the same patient. We therefore decided to investigate drug effectiveness in suppressing gastric secretion with that dose which produced acceptable, constant, comparable, and tolerable side-effects. The dose adopted was one increment below that which uncomfortable symptoms of parasympathetic inhibition were produced, such as blurring of vision, palpitation, dizziness, headache, weakness, flushing of the face, and/or excessive dryness of the mouth and throat. This we termed the "optimal effective dose" (O. E. D.). With it, we found tricyclamol methylsulfate to be effective in suppressing gastric acidity to pH 4.5 or higher in all 16 patients; mepiperphenidol bromide, in all 13 tested; propantheline bromide, in 11 of 12, and belladonna tincture in only 2 of 5 patients. Although the intensity of secretory inhibition after a single O. E. D. of these drugs varied from patient to patient, results were reproducible in the same patient.[1] The optimal effective dose and the dose calculated in terms of milligrams per kilogram of body weight for tricyclamol methylsulfate, mepiperphenidol bromide, and propantheline bromide varied considerably from patient to patient (Table 2). In order

to administer an effective dose, therefore, one needs to tailor the dose of the drug to each patient and not administer it according to body weight or any recommended uniform dose.

Since "inhibition of 'basal' gastric secretion does not necessarily signify a similar lowering of the 'digestive' secretion characterizing the usual clinical condition," [6] an hourly pH study of the gastric secretion throughout day and night was done with the drug when the patient was on a rigid ulcer diet of milk and cream mixture (Schedule A). The results show that the hourly feeding of this mixture was ineffective in controlling the acidity of the gastric contents, especially during the night. The addition of the "recommended" dose (50 mg.) of tricyclamol methylsulfate to the milk and cream mixture (Schedule B) did not materially affect the acidity. The optimal effective dose of tricyclamol methylsulfate (Schedule C), however, efficiently controlled acidity in four of the eight patients. Night secretion was adequately controlled by an additional O. E. D. of tricyclamol methlysulfate at 3 : 30 a. m. Aluminum hydroxide and magnesium trisilicate alone (Schedule D) was less effective. In the other four patients the O. E. D. of tricyclamol methylsulfate did not reduce the acidity of the gastric contents, while the aluminum hydroxide and magnesium trisilicate mixture was partially effective. These different patterns of response might be explained by individual differences in the rate of secretion and in the relative prominence of neurogenic and hormonal stimuli. The combined use of the O. E. D. for tricyclamol methylsulfate and aluminum hydroxide and magnesium trisilicate mixture (Schedule E) served best in this type of response to diminish the acidity of the gastric contents. Similar patterns were also observed with mepiperphenidol bromide.

The effectiveness of the O. E. D. (250 mg.) of tricyclamol methylsulfate and its superiority over the "recommended" dose (50 mg.) in Patient E. M. for inhibiting gastric secretion induced by emotional stress (Figs. 5 and 6) further illustrate the value of the O. E. D., the "tailored" dose. Preliminary results of studies on the effect of anticholinergic drugs on gastric secretion induced by insulin hypoglycemia showed that the O. E. D. of an effective drug could produce a pronounced inhibition of the late phase, the adrenal phase, of gastric secretion in some patients. These results, if borne out by further studies, would indicate that these compounds, in addition to their ability to partially inhibit vagal secretion induced by insulin hypoglycemia, can also inhibit the adrenal phase of gastric secretion.

Dryness of the mouth and slight increase in pulse rate, the latter in some of the patients, were the only side-effects observed during prolonged administration of the O. E. D. of these drugs. There was no change in blood pressure in both the sitting and the erect positions. Only in an occasional patient did dryness of the mouth and throat become objectionable enough to necessitate the reduction of the dose by an additional increment. Administered after a meal, these drugs can be given in doses one increment higher than if given before meals, to produce essentially the same side-effects, the difference obviously dependent upon different rates of absorption under the two conditions of administration. Anticholinergic drugs are contraindicated in the presence of prostatic hypertrophy, incipient glaucoma, and organic pyloric obstruction. Pretreatment and follow-up studies of blood cell count, urine analysis, blood urea nitrogen, renal phenolsulfonphthalein-excretion test, and hepatic function tests showed no changes during prolonged administration of the O. E. D. of effective drugs.

The uniformity of our results showing inhibition of basal gastric secretion to pH 4.5 or higher by a single optimal effective dose of an active anticholinergic drug and its superiority over a single "recommended" dose in inhibiting "digestive" gastric secretion, secretion induced by emotional stress, and insulin hypoglycemia present a case for the use of the optimal effective dose of these drugs in the clinical management of peptic ulcer disease, if elimination of peptic activity is a *sine qua non* for complete healing of

the ulcer. The absence of any untoward side-effects on prolonged administration of the O. E. D. of these drugs makes this dosage schedule practical for clinical use. The "recommended" dose of these active drugs was ineffective in suppressing basal gastric secretion in most cases and often added nothing to the milk and cream mixture in suppressing "digestive" secretion. In a disease such as peptic ulcer whose natural life history is characterized by relapses and remissions, the doctor must especially avoid deluding himself by always attributing what might be a spontaneous remission to the treatment given. We have heard it argued that the administration of anticholinergic drugs, in doses that must have been inadequate to influence gastric secretion, had been responsible for the remission of the ulcer attack. If we are to believe that valid ulcer therapy must achieve and maintain a clinical anacidity at which point peptic activity is reduced to a minimum (pH 4.5), the proteolytic endpoint of Hollander, then that dose of a drug which fails to produce even a pH 3.5 (Töpfer's anacidity) can hardly be conceived to be altering intragastric conditions that could bring about healing of the ulcer.

We found in three patients with active duodenal ulcer, studied on the series of schedules listed, that symptoms, especially night pain, were not relieved on the day when milk and cream mixture alone (Schedule A) was administered, nor on successive days with the "recommended" dose of the drug (Schedule B) or AMT (Schedule D), but did disappear on the day the O. E. D. (Schedule C) was administered. Withdrawal of the O. E. D. of the drug resulted in a recurrence of symptoms, which again on successive days were not relieved by milk and cream mixture alone, the "recommended" dose of the drug and/or AMT but were relieved by the O. E. D. We would emphasize that these studies are specifically concerned with the evaluation of anticholinergic drugs in patients with peptic ulcer but that these drugs comprise only a part of the over-all managment of the disease.

On the basis of the experiments of hourly pH study, we now use the optimal effective dose of active anticholinergic drugs, four times daily, before each meal and at bedtime, and where possible an additional dose at 3:30 a. m., together with aluminum hydroxide and magnesium trisilicate mixture given at two-hour intervals from 8 a. m. to 12 midnight. It is obvious that a truly long-acting preparation of an effective anticholinergic drug would be very useful toward the control of night secretion. At the present time we are experimenting with a schedule in which the patient with peptic ulcer continues to take these drugs for six months or until two months after the next expected seasonal relapse in those patients with regular recurrences.

If, as is currently generally accepted, the acid-pepsin factor is the ultimate determinant for the development and recurrence of peptic ulcer and if psychogenic factors, so important in the peptic ulcer patient, act deleteriously by stimulating gastric secretion and perhaps, too, encourage local mucosal damage through epinephrine, that appears to be released in the process responsible for the adrenal phase of gastric secretion,[3] then the results of our studies indicating the value of the optimal effective dose of anticholinergic drugs suggest an approach to the control of gastric acidity throughout the 24-hour period. This, used in conjunction with other measures to control acidity, introduces a possible attack on that very urgent problem for the peptic ulcer patient, the prevention of recurrence, which present medical management fails to achieve significantly.

SUMMARY AND CONCLUSIONS

If optimum conditions for the healing of an ulcer are to be achieved, peptic activity must be inhibited. We selected the duration of suppression of gastric acidity to pH 4.5 or higher as the main criterion for judging significant antisecretory potency, since at pH 4.5 peptic activity is reduced almost to zero. For comparison of relative effectiveness of different anticholinergic drugs in suppress-

ing gastric secretion, the dose adopted was one increment below that which produced uncomfortable symptoms of parasympathetic inhibition. This dose we termed the optimal effective dose (O. E. D.).

The effect of four compounds on basal gastric secretion was investigated in 22 patients with chronic duodenal ulcer. The O. E. D. of the anticholinergic drugs tested suppressed gastric acidity, producing pH values of 4.5 or higher uniformly, except when belladonna tincture was used, which produced similar results in only two of five patients. The optimal effective dose and the dose calculated in terms of milligrams per kilogram of body weight for these drugs varied from patient to patient and independently of each other. To administer an effective dose of these drugs, one has to tailor the dose to each patient and not administer it according to body weight or any recommended dose.

Hourly pH studies of the gastric contents throughout day and night in patients with ulcers on a diet of a milk, cream, and skim milk powder mixture alone and in combination with a mixture of aluminum hydroxide and magnesium trisilicate (AMT) and/or one "recommended" dose of tricyclamol (Elorine) methylsulfate or mepiperphenidol bromide failed to control gastric acidity satisfactorily. The use of the optimal effective doses of tricyclamol methylsulfate and mepiperphenidol bromide produced satisfactory results in half the patients studied. The pH of the gastric contents remained at 4.5 or higher for variable periods during day and night. Night secretion was controlled materially by giving an additional optimal effective dose of the drug at 3: 30 a. m.

The uniformity of our results showing an inhibition of basal gastric secretion to pH 4.5 or higher by a single optimal effective dose of an active anticholinergic drug and its superiority to a single recommended dose in inhibiting "digestive" gastric secretion and secretion induced by emotional stress and by insulin hypoglycemia present a case for the use of the optimal effective dose of these drugs in the clinical management of peptic ulcer disease. The absence of any untoward side-effects following prolonged administration of the optimal effective dose of these drugs makes it practical for clinical use. The "recommended" dose of these active drugs was ineffective in suppressing basal gastric secretion in most cases and often added nothing to the milk and cream mixture in suppressing "digestive" secretion. The effectiveness of these drugs when used in proper dosage may offer an approach to a regimen designed to prevent ulcer recurrence.

R. Smiley Pattinson, B.S., M.T. (A.S.C.P.), gave technical assistance. Eli Lilly & Company provided the tricyclamol (Elorine) methylsulfate; Sharp & Dohme, Division of Merck & Co., Inc., the mepiperphenidol (Darstine) bromide; G. D. Searle & Co., the propantheline (Probanthine) bromide, and Wyeth Laboratories, Inc., the aluminum hydroxide and magnesium trisilicate (AMT) mixture used in this study.

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Treatment in Internal Medicine

THE MODERN TREATMENT OF THYROTOXICOSIS

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SINCE thyrotoxicosis was first described, in 1786 by Parry [1] and later by Graves,[2] many methods of treatment have been used in this disease. Although iodine was first recommended as a therapeutic agent in 1820 by Coindet,[3] it was not until 1923 that Plummer [4] demonstrated its ability to diminish the activity of the hyperfunctioning thyroid gland and its usefulness in preoperative preparation. X-ray treatment had been tried extensively after 1900,[5] but, although effective in some cases, it gradually went into disuse. Iodine alone or followed by subtotal thyroidectomy was used almost exclusively until the early 1940's, when the thiourea derivatives were found useful in preparation for surgery as well as in cases where "medical thyroidectomy" was desirable.[6] The most recent advance in the therapy of thyrotoxicosis has been the use of radioactive iodine, first reported effective in 1942.[7] The current concepts of therapy in thyrotoxicosis will be presented as modified by our own experiences.

CLASSIFICATION OF THYROTOXICOSIS

I. Diffuse Toxic Goiter (Graves' Disease)
  A. Typical
  B. Atypical
    1. Without exophthalmos
    2. Without clinically apparent goiter
    3. Exophthalmos without apparent hypermetabolism
    4. With nodules
    5. Malignant exophthalmos and pretibial myxedema
II. Nodular Toxic Goiter
  A. Typical
  B. Toxic nodules without apparent hypermetabolism
  C. Thyrocardiac disease
III. Recurrent Thyrotoxicosis

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I. Thyrotoxicosis may be divided into two types, diffuse toxic goiter and nodular toxic goiter, which are probably not etiologically related. Diffuse overactivity of the thyroid gland (Graves' disease) classically has the findings of thyrotoxicosis and exophthalmos. The thyroid gland is almost always enlarged, usually without nodules. Atypical forms of this disease occur frequently. Many cases of diffuse thyrotoxicosis are seen without exophthalmos, while still others are found in which no goiter can be palpated. Occasionally, Graves' disease may present as exophthalmos with little clinical evidence of hypermetabolism although laboratory tests, particularly radioactive-iodine studies, demonstrate hyperactivity of the thyroid gland.

CASE 1.—*Diffuse thyrotoxicosis with nodules and without exophthalmos*

A 44-year-old white woman with an enlarged thyroid gland containing two discrete palpable nodules had symptoms and findings of thyrotoxicosis without exophthalmos. Laboratory studies showed an I^{131} uptake of 59% in 24 hours; the conversion ratio $\left(\frac{PBI^{131}}{\text{Plasma } I^{131}} \times 100\right)$ was 77%; serum cholesterol was 155 mg. per 100 cc.; serum protein-bound iodine (PBI) was 10.2γ per 100 cc., and the BMR was +37%. Differential scanning of the thyroid area revealed a low accumulation of I^{131} over the nodules, with a generalized increase in I^{131} uptake in the remainder of the gland (Fig. 1).

This demonstrates that the thyrotoxicosis was due to diffuse hyperactivity rather than to the presence of toxic nodules. This is a common problem in an endemic goiter area and can be diagnosed only if differential thyroid scanning following I^{131} administration shows diminished activity in the

Fig. 1 (Case 1).—Graphic depiction of radioautograph of the thyroid gland, showing markedly diminished radioactivity in the area of the nodules.

area of the nodule as compared with the remainder of the gland. In the presence of exophthalmos, diffuse thyrotoxicosis may be presumed to exist even without the use of differential scanning techniques.

Malignant exophthalmos and pretibial myxedema are complications of toxic diffuse goiter and may occur while signs and symptoms of thyrotoxicosis are being controlled by therapy. Malignant exophthalmos is manifested by increasing protuberance of the eyes, periorbital edema, chemosis, dilatation of conjunctival vessels, and increased retroorbital pressure frequently accompanied by visual disturbances, most commonly diplopia. Pretibial myxedema may accompany malignant exophthalmos and is characterized by localized brawny edema, usually on the anterior aspect of the legs. Although Beierwaltes [8] reported pretibial myxedema in 7 of 28 patients with malignant exophthalmos, in our experience this manifestation is relatively uncommon.

II. Nodular thyrotoxicosis is due to one or more hyperactive nodules. Exophthalmos rarely, if ever, occurs in these cases, and thyroid tissue which is not included in the nodule or the immediately adjacent area is frequently found to be hypoactive by differential scanning techniques. Some of these cases may be considered latent in that the total metabolism may be normal or only slightly elevated, but the conversion ratio indicates the presence of hyperactive thyroid tissue.

CASE 2.—*Toxic nodule without apparent hypermetabolism*

A 35-year-old white woman with recent enlargement of a solitary thyroid nodule which had been present for five years showed no evidence of thyrotoxicosis by history or physical examination. Thyrotoxicosis had not been found on previous evaluation elsewhere. Results of studies of thyroid function were as follows: B. M. R. +7%; cholesterol, 230 mg. per 100 cc.; PBI, 5.5γ per 100 cc.; thyroid uptake of I^{131} in 24 hours, 32%. But the conversion ratio was 72% (normal, 10% to 20%), indicating increased conversion of inorganic iodine to thyroid hormone. Differential scanning of the thyroid after I^{131} tracer dose showed nearly all of the radioactivity concentrated in the area of the nodule (Fig. 2). This was interpreted to mean that the hyperactive nodule secreted sufficient thyroid hormone to inhibit the function of the remainder of the gland by inhibiting the pituitary gland. The net result was normal thyroid hormone production and normal metabolism.

This is an example of a hyperactive nodule depressing the function of the residual normal thyroid tissue. It is probable that in this type of case clinical thyrotoxicosis would eventually develop if untreated.

Another form of thyrotoxicosis, more apt to occur in older age groups, is thyrocardiac disease without apparent hypermetabolism (masked thyrotoxicosis). It is more frequent in toxic nodular goiter but may be

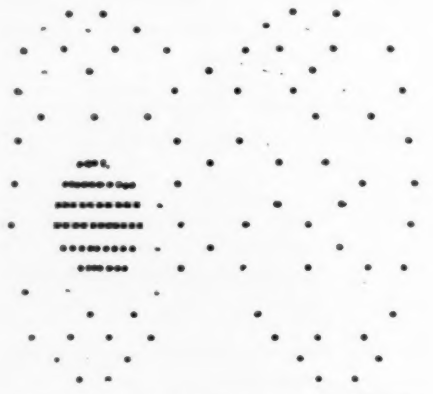

Fig. 2 (Case 2).—Graphic depiction of radioautograph of the thyroid gland, showing increased radioactivity in the area of the solitary nodule as compared with the remainder of the gland.

associated with diffuse thyrotoxicosis. Because of the frequent presence of congestive heart failure and impaired renal function, many of the usual indices of thyrotoxicosis (B. M. R., radioactive iodine, cholesterol) may be unreliable. Needless to say, to make this diagnosis a high index of suspicion and reliance on other evidence of thyrotoxicosis is needed. In our experience, the PBI and conversion ratio have been the most dependable laboratory aids. Although any form of heart disease may be mimicked and bizarre cardiac murmurs may be found, cardiac arrhythmias, particularly auricular fibrillation, may be the only clinical manifestation.

III. Thyrotoxicosis may recur after any type of therapy other than total extirpation of the thyroid. It is frequently difficult to ascertain whether this is due to incomplete initial therapy or is a recurrence of the original disease.

FORMS OF MODERN THERAPY IN THYROTOXICOSIS

I. Medical therapy
  A. General
    1. Nutrition
    2. Sedation and rest
  B. Iodine
  C. Antithyroid drugs—propylthiouracil, methimazole (Tapazole)
II. Surgical—Subtotal thyroidectomy
III. Radiation
  A. X-ray
  B. Radioactive iodine

I. MEDICAL THERAPY

A. General Therapy

Innumerable reports have been presented in the literature in regard to the abnormal nutritional requirements of patients with thyrotoxicosis. These revolve about the deficiencies in caloric intake; the usual negative nitrogen, calcium and phosphorus balances, and the increased requirements for vitamins, particularly, A, the B group, and C.* Formerly, when the diagnosis of thyrotoxicosis frequently was delayed and attempts at therapy were relatively inadequate, the nutritional factors were of tremendous importance. As thyrotoxicosis is now being recognized at earlier stages in the disease and more effective therapy instituted sooner, these factors are diminishing in significance. This is very similar to the change in the approach to the treatment of infectious diseases, where general measures assume less importance with the use of effective specific measures.

An exception to this should be noted in the elderly woman, in whom masked hyperthyroidism may result in severe osteoporosis with compression fractures owing to the above-mentioned nutritional disturbances and the delay in diagnosis.† It is suggested, therefore, that tests of thyroid function be performed in all elderly patients with osteoporosis.

Since excessive amounts of thyroid hormone sensitize the individual to produce exaggerated physiological responses to normal stresses of day-to-day living, sedation and rest have been demonstrated to be an extremely important part of the therapy while the patient is in the process of being controlled by specific treatment. It has been demonstrated repeatedly that patients with thyrotoxicosis tolerate much higher doses of sedation than the nontoxic person. Therefore, the amount of sedative to be used cannot be predetermined, but the optimum dose must be found for each patient.

B. Iodine

The thyroid has a high avidity for iodine, concentrating approximately 20% of the total body stores.[17] Iodine is absorbed from the intestinal tract as iodide and is removed from the blood stream by the thyroid epithelium in that form. In the cells of the thyroid gland iodide is converted to nascent iodine by an enzymatic process and is then combined with tyrosine to form diiodotyrosine. Two molecules of diiodotyrosine combine to form thyroxin, which, in turn, combines with a protein to form thyroglobulin. Thyroglobulin may be stored in the thyroid follicle or be reconverted in the

* References 9-14.

† References 13-16.

cells to thyroxin and released into the blood stream. Iodine may also become fixed in the thyroid without combining organically.

Iodine, thus, is essential in the formation of thyroid hormone. In addition, it causes involution of the thyroid cells, particularly when they are hyperplastic, inhibits the release of thyroxin from the thyroid, and may also inhibit the pituitary secretion of thyroid-stimulating hormone (TSH).[17] It is because of these effects that iodine is beneficial in thyrotoxicosis.

Iodine as the sole treatment of thyrotoxicosis has been found effective only in milder cases, where it may induce an euthyroid state and, rarely, hypothyroidism. In severer cases, partial or transient relief is the rule. Even in mild cases the effect of iodine is frequently temporary. Recurrence of toxicity may develop as long as several years after apparent control.

Iodine has its widest application in the preparation of patients for thyroidectomy. In mild thyrotoxicosis iodine alone for 7 to 21 days may provide adequate preparation. However, if it is given for too prolonged a period a reduction in the beneficial effects may occur. Consequently, its use is usually limited to patients who have been rendered euthyroid or nearly so by antithyroid drugs in preparation for thyroidectomy. Iodine is invaluable to the surgeon in causing involution and decreased vascularity of the thyroid gland, especially after treatment with antithyroid preparations. Strong iodine solution U. S. P. (Lugol's solution) is the most widely used form of iodine, although other preparations containing organically bound iodide in tablet form are available which may be less disagreeable to the patient and produce less gastric irritation. Strong iodine solution U. S. P., equally effective in diffuse and nodular goiter, is usually given in doses of 5 to 15 drops (0.3 to 0.9 cc.) two or three times daily.

Iodine uncommonly produces undesirable side-reactions, including nasal congestion; tearing; acne; increase in size of salivary glands, particularly the parotids, and dermatitis. Rarely, an exfoliative dermatitis is produced which may prove fatal.

C. Antithyroid Drugs

Many substances have been found to be antithyroid by inhibiting the formation or release of thyroxine. Those most useful clinically are a thiourea derivative, propylthiouracil, and methimazole. The effect of these compounds is due to interference with iodinization of tyrosine in the production of thyroxine. They do not inhibit, but may increase, the trapping of iodine by the thyroid. These substances are goitrogenic since, with decreased production or release of thyroxine, anterior pituitary inhibition is decreased. Consequently, larger amounts of thyrotropic hormone are released, which produces a vascular, hyperplastic thyroid gland.

Administration of these substances in sufficient amounts over a prolonged period produces a decrease in metabolism and may occasionally result in hypothyroidism. The usual response to treatment is a reduction in all signs of toxicity, but frequently enlargement of the thyroid or increasing exophthalmos may be noted. To avoid this, treatment with desiccated thyroid may be given concurrently with the antithyroid drug to inhibit the production of thyrotropin. Antithyroid preparations are effective in both diffuse and nodular toxic goiters. The response in diffuse toxic goiter averages 1% reduction of the B. M. R. daily, and the response in nodular goiter is a little less. However, there are wide individual variations. The usual dose of propylthiouracil is between 200 and 400 mg. daily in divided doses, and that of methimazole is 20 to 40 mg. daily. A few cases are resistent to these medications because of inadequate dose or prior treatment with iodine preparations or because sufficient time is not allowed for the previously stored hormone to be completely utilized. In resistant cases larger amounts of medication, as much as 1000 mg. of propylthiouracil daily, may be necessary to achieve the desired effect.[18]

The use of antithyroid drugs and iodine has made emergency thyroid surgery obso-

lete, and surgery is contraindicated until thyrotoxicosis is well controlled. As a result, when used as preoperative preparation these compounds should be given until a state approximating euthyroidism is reached. At that time an iodine preparation is given for 7 to 21 days prior to surgery in order to produce involution of the thyroid. The antithyroid drugs may be continued during the period of iodine therapy. Clinically, the most useful signs of control and, consequently, operability are a definite gain in weight and reduction of the pulse to below 100.

Propylthiouracil and methimazole may be used as definitive therapy in both nodular and diffuse thyrotoxicosis. Prolonged administration for at least six months and usually for more than one year is necessary to achieve lasting results. Various observers have reported prolonged remission in from 14% to 67.4% of cases treated with these drugs.‡ Although other measures are more effective as the sole means of therapy, the exclusive use of antithyroid agents may be warranted in certain cases such as nodular goiters and aged persons who are poor surgical risks, if I^{131} is not available.

These medications produce toxic reactions with sufficient frequency to warrant careful observation of patients so treated. The commonest reactions are dermatitis, leucopenia, agranulocytosis, drug fever, and, very rarely, hepatitis. Bartels [25] reported an incidence of toxicity with propylthiouracil of 1.8% in 820 cases, most of which were treated for comparatively short periods. Agranulocytic reactions occurred in only about 0.1%. The toxicity of methimazole is somewhat higher, but, while Chevalley and McGavack reported an over-all incidence of 4%,[26] they believe that the more serious toxic reactions, particularly agranulocytosis, occur about equally with the two compounds.[27] The majority of reactions are mild dermatidities which clear rapidly when medication is discontinued. Blood cell counts should be performed frequently in patients who are taking these medications, although the onset of agranulocytosis may be so sudden that adverse reactions may be detected as readily by symptoms as by weekly blood counts. In the interest of conservatism, we obtain blood cell counts every two weeks during the initial two months and then at monthly intervals.

‡ References 19-24.

II. SURGERY

Although in the past many surgical approaches to the control of thyrotoxicosis were tried, including ligation of thyroid arteries and multistage resections of thyroid tissue, bilateral subtotal thyroidectomy has become the procedure used almost exclusively at present. With the combined use of antithyroid drugs and iodine, or iodine alone, as preoperative preparation, subtotal thyroidectomy has become a safe and effective means of treating thyrotoxicosis. It is a compliment to our surgeons that they have been able, with experience, to judge precisely the right amount of tissue to be removed in so large a number of cases.

As surgical technique has improved complications from thyroidectomy have progressively decreased. Pemberton [28] reported only 2 deaths in 1107 cases. Cattel [29] reported 4 deaths in 1730 cases, or an incidence of 0.2%, at Lahey Clinic. Goldman [30] reported 0.5% mortality in toxic nodular goiters and 1% mortality in toxic diffuse goiters, most of which were operated on by resident staff members. The incidence of permanent recurrent laryngeal nerve injury has been reported to be between 0.4% and 2%,§ with temporary paralysis occurring in between 3% and 5.3%. Permanent hypoparathyroidism of some degree occurs in 0.2% to 5% of the cases,‖ and transient hypoparathyroidism occurs in an additional small percentage. Serious postoperative hemorrhage or tracheal obstruction occur uncommonly and can usually be combatted successfully. Thyrotoxic crisis following surgery has become rare with adequate preoperative preparation.

Hypothyroidism following subtotal thyroidectomy has occurred in from 4.5% to

§ References 29-32.

‖ References 29, 30, 32, and 33.

29.7% of the cases,¶ the over-all incidence being closer to the lower figure. Hypothyroidism, though undesirable, is not a serious complication and is readily amenable to treatment with 60 to 180 mg. of desiccated thyroid or its equivalent daily.

The incidence of persistent thyrotoxicosis following subtotal thyroidectomy depends on the completeness of the procedure and varies from 1.7% to 18.5%,# but it is generally in the neighborhood of 3%. Persistence represents failure of the treatment and necessitates either reoperation or the use of other forms of therapy. Recurrence of thyrotoxicosis has been reported in from 1% to 6.8%,* but most observers have reported an incidence of 2% to 3%. Reoperation in either persistent or recurrent thyrotoxicosis increases the incidence of all complications.

It may seem repetitious to state that the statistics of surgical achievements are usually presented from areas where a high degree of skill and efficiency has been achieved. These statistics have also been achieved by excluding patients with severe complicating diseases in which the hazards of surgery were deemed too great.[36] It is doubtful that this extremely low mortality and the moderate incidence of complications could be equalled by surgeons whose experience is limited to an occasional thyroidectomy. Therefore, the selection of optimum therapy will depend on the availability of highly skilled teams experienced in the problems posed by thyroid surgery.

III. RADIATION

External radiation of the thyroid was first attempted in 1902 [5] and subsequently was widely used prior to the advent of iodine. In general, cure was effected in one-third of the cases of thyrotoxicosis; improvement, in one-third, and no effect, in one-third. The milder the case the more apt the treatment was to be effective. Soley and Stone [37] reported remission in 58% of 48 cases, but most observers have not been so successful.[38] Frequent recurrences or exacerbations have been reported, although the period of treatment has lasted as long as nine months. The major limiting factor in the use of external irradiation is the difficulty in obtaining sufficient radiation to the thyroid without producing serious damage to the skin or surrounding tissues.

With the advent of the radioactive isotopes of iodine, a method of achieving adequate localized radiation to the thyroid was found, utilizing the avidity of the thyroid for iodine and the rapid excretion of iodine not trapped in the thyroid. Although normally only about 20% to 30% of the administered iodine is held in the thyroid, this percentage is usually much higher in thyrotoxicosis. The radiation effect of I^{131}, the isotope used almost exclusively at the present time, is due primarily to the action of beta rays, which have an effective range of 2 mm. or less in soft tissue. Approximately 10% of the radiation is due to the more penetrating gamma rays. However, the gamma rays emitted by the doses used in the treatment of thyrotoxicosis produce little demonstrable radiation effect to the tissues outside of the thyroid. The physical half-life of this isotope, eight days, is appreciably diminished in the body owing to physiological and excretory factors. The effective half-life within the body is called the biologic half-life. The amount of effective radiation delivered to the thyroid gland depends upon the biological half-life of I^{131}, usually about six days. In a few patients it may be as little as three to four days, thus appreciably reducing the amount of effective radiation received by thyroid tissue. The sensitivity of thyroid cells to radiation varies with the degree of cellular hyperplasia present. Agents which reduce hyperplasia, such as iodine, may decrease the effectiveness of radiation. Some patients who have received these substances over a prolonged period have been found comparatively radioresistant. Decrease in metabolism after I^{131} is not ordinarily observed until about three weeks after the administration of a therapeutic dose, but it

¶ References 29, 30, and 33.

References 33-35.

* References 33 and 34.

is usually progressive after this time. Although no appreciable radiation can be found in the thyroid after one month, diminution of thyroid function may continue for as long as four to six months after a dose of I^{131} has been given.

Chapman and Maloof [39] reported cure of thyrotoxicosis with one dose of I^{131} in 391 of 520 patients with both nodular and diffuse goiters. Fifty-one of their patients required two doses; nine required three doses, and two required four doses. Thirty-five deaths occurred before sufficient time had elapsed for adequate evaluation, none of which were attributable to the treatment. The remaining 32 patients were improved but not cured, had surgery performed, or were lost to follow-up. These authors reported no serious complications, although occasional thyroiditis was noted. Myxedema was found in 8% of their series, and in only one case, that of a nodular goiter, was there recurrence.

TABLE 1.—*Thyrotoxicosis Treated with I^{131} in the Division of Endocrinology and Metabolism, the Ohio State University* *

Type of Thyrotoxicosis	Patients Treated, No.	Patients Requiring More Than One Treatment, %	Patients with Hypothyroidism (Temporary or Permanent), %
Diffuse	77	23.4	18.2
1 dose	59		17.0
2 doses	15†		26.6
3 doses	3		0.0
Nodular	28	39.3	7.1
1 dose	17‡		6.0
2 doses	10		10.0
3 doses	1		0.0
Recurrent	16	37.5	12.5
1 dose	10		10.0
2 doses	5		20.0
3 doses	1		0.0
Total	121	29.0	14.8

* Twelve patients treated with I^{131} for nonthyroid cardiac disease are not included in this table.
† One patient was improved after two doses but desired surgery.
‡ Two patients underwent surgery.

Of 207 patients to whom we have given therapeutic I^{131}, follow-ups have been unobtainable in 19 cases and 55 cases have been followed for less than six months from their last dose. Of the 133 cases considered completed with periods of observation from six months to five years after treatment (Table 1), 77 had diffuse thyrotoxicosis, 28 had nodular thyrotoxicosis, 16 are cases in which subtotal thyroidectomy has been followed by recurrence of thyrotoxicosis, and 12 were euthyroid but were treated for severe cardiac disease. It is our practice to routinely reexamine patients treated with I^{131} at three-month intervals until they have become euthyroid and then at six-month intervals for at least two years following therapy.

Our selection of cases originally included only patients over the age of 40 years with diffuse thyrotoxicosis. More recently we have been treating many younger patients, especially if there have been associated medical disorders that increased the surgical risk or severe exophthalmos, or if the patient refused surgery. No patients were treated with I^{131} if they were known to be pregnant. Thus our series includes patients from 15 to 74 years of age.

Selection of the dosage of I^{131} to be used has depended upon the estimated size and weight of the gland and the thyroid uptake of I^{131} as determined by tracer doses. The weight of the thyroid may be difficult to evaluate, experienced observers having an error of as great as 50%. Consequently, we have not attempted to judge the exact amount of radiation delivered per gram of thyroid tissue. Our dosage range for initial treatment has varied between 4 and 10 mc. of I^{131}, and at the present time it is usually between 6 and 8 mc. With experience greater success has been achieved in selecting the optimum dose for each individual patient.

In deciding whether a second dose should be given, the degree of improvement in the patient's signs and symptoms three months after the treatment is the determining factor. If the patient has become euthyroid or has improved markedly, no further treatment is given and the patient is reevaluated in three months. However, if there is no improvement or only limited improvement, or if initial improvement has been followed by a return of symptoms, an additional dose of I^{131} is given.

Patients receiving a second dose of I^{131} usually are given a smaller amount, between 2 and 6 mc. unless the initial treatment has had no apparent effect on the thyroid. In retrospect, three cases that became hypothyroid after two doses of I^{131} given at three-month intervals might have become euthyroid without a second dose of I^{131} if observed over a longer period of time. Four cases required three doses. However, in our experience no cases have occurred that could not eventually be controlled if sufficient I^{131} was given.

A. Diffuse Thyrotoxicosis

Seventy-seven patients with diffuse thyrotoxicosis are included in this study. Eighteen were males, and fifty-nine were females. All of these are euthyroid or hypothyroid following therapy with I^{131}. Fifty-nine patients received one dose of I^{131}, of which forty-nine have become euthyroid and ten have had either transient or permanent hypothyroidism requiring thyroid replacement therapy. Fifteen cases have required two doses of I^{131}, following which four developed hypothyroidism. One case was only partially improved after two doses and preferred to have surgery rather than a third dose of I^{131}. Three cases required three doses of I^{131}. None of these cases have had recurrence of thyrotoxicosis.

B. Nodular Thyrotoxicosis

Toxic nodular goiters respond less predictably to I^{131} and, ordinarily, require larger doses than do diffuse goiters. We consider subtotal thyroidectomy a more preferrable form of treatment in the majority of these cases and consequently have treated only those who refused surgery, were poor surgical risks because of age or complicating disease, or were judged candidates for preparation for surgery with I^{131}. Of the 28 cases in this group, 17 received one treatment with I^{131}, 10 received two treatments, and 1 received three treatments. There were 23 women and 5 men, varing in age between 28 and 78 years. One patient became hypothyroid after one treatment and one became hypothyroid after two treatments. Some of the patients may have had diffuse thyrotoxicosis without exophthalmos with incidental thyroid nodules not related to the disease, in which case they are erroneously included in this group. Two patients receiving two doses of I^{131} improved, but they remained toxic and eventually underwent surgery.

The initial treatment of these cases has varied between 8 and 10 mc., depending on the size of the gland and the thyroid uptake of I^{131}. Second doses have been of the same order.

C. Recurrent Thyrotoxicosis after Thyroidectomy

I^{131} is an effective means of treating postoperative recurrent thyrotoxicosis, and our series includes 16 cases in this category, of which 2 were males and 14 were females. Ten of these received one dose; five received two doses, and one required three doses. Hypothyroidism occurred in one receiving one dose and one receiving two doses. The determination of the dose is based on the same criteria used in the treatment of diffuse thyrotoxicosis.

D. Euthyroid Cardiacs

The use of I^{131} in euthyroid patients with cardiac disease has recently been under investigation. In cases of severe angina or congestive failure unresponsive to usual measures reduction of thyroid function relieves the cardiac work load and may cause temporary improvement. Blumgart, Freedberg, and Kurland,[40] in summarizing the results in 1070 cardiac patients, found moderate or marked improvement in 75% of patients with angina pectoris and 60% of patients with congestive failure. Jaffe, Rosenfield, Pobirs, and Stuppy,[41] in a series of 231 patients, reported improvement in 93% of patients with angina and in 81% of patients with congestive failure.

The methods of therapy have varied, the recommended total dosage of I^{131} being as high as 50 mc., usually given in divided doses over several weeks to avoid sudden release of

stored thyroid hormone because of radiation thyroiditis.

This procedure is primarily palliative, since there is no evidence that life expectancy is prolonged. Sufficient time to evaluate the effects of the induced hypothyroidism upon the primary pathological processes in the heart or blood vessels is lacking. As a result, only cases in which the prognosis is very poor and which have not responded to any known pharmacological or medical therapy have been treated.

In our own limited experience of 15 cases adequate follow-up has been obtained in 12. The dosage of I^{131} has been small, usually no more than 10 to 12 mc., and a second dose has been given in only four cases. Of the eight patients with angina, seven were at least temporarily improved, although four have died. Three of the four cases with congestive failure have died, but only one case did not show some temporary improvement prior to death. It is doubtful that the longevity of any of our patients has been altered.

E. Complications and Toxic Effects of I^{131}

A discussion of the complications of the use of I^{131} in the treatment of thyrotoxicosis must be divided into two distinct categories: (1) the demonstrated or observed complications and (2) the theoretical complications.

(1). Observed Complications.—Recurrence of thyrotoxicosis has been reported only rarely following treatment with I^{131}. We have observed no cases of recurrence in our series.

Hypothyroidism, either temporary or permanent, occurred in 18.2% of our diffuse toxic goiters, 7.1% of nodular toxic goiters, and 12.5% of recurrent thyrotoxicosis, with a total incidence of 14.8%. Our incidence of permanent hypothyroidism is 10.8%. Chapman and Maloof [39] reported an incidence of myxedema of 8%. Clark and Rule [42] reported varying degrees of hypometabolism in 17.2% of 628 patients treated with I^{131}.

Toxic effects of radioactive iodine have been reported uncommonly and have included acne and gynecomastia.[43] This has not been noted in any of our patients. Hypoparathyroidism has been reported in one case treated with I^{131}. This case had been subjected to subtotal thyroidectomy prior to treatment. No alteration in calcium or phosphorus serum levels has been observed in any of our treated patients. The blood picture is not altered by the amount of radioactivity used in the treatment of thyrotoxicosis. The amount of iodine given is so minute that toxic reactions do not occur even in patients who are known to be sensitive to iodine. Radiation sickness has not been reported following I^{131} treatment of thyrotoxicosis. Radiation thyroiditis or parotitis manifested by tenderness over the thyroid or salivary glands occurs in the first few days following treatment in a relatively few patients. This has been controlled easily by the use of analgesics for three to five days.

Infrequently, in an extremely toxic person sufficient damage may occur to cause excessive release of thyroglobulin into the blood stream, producing an exacerbation of the thyrotoxicosis and, rarely, thyroid storm. We have had minor exacerbations occur in two patients, both of whom responded promptly to sedation and iodine. The occurrence of exacerbations of thyrotoxicosis or thyroid storm can be avoided by the administration of strong iodine solution U. S. P., starting four days after the administration of the dose of I^{131}, although we have seldom found this necessary.

(2) Theoretical Complications.—(*a*) The major limitation to the general use of I^{131} in the treatment of thyrotoxicosis has been the theoretical possibility of the later development of malignancy in the thyroid gland. Although experience has been obtained over more than a 14-year period, no cases of malignancy due to radioactive iodine have been reported in humans. That this will occur in the future seems unlikely, although at the present time it is impossible to state conclusively that this may not happen.

Various animal studies have been performed which suggest that the malignant

changes observed in rats following I^{131} may be due to hormonal factors rather than direct radiation effect. Thyrotropin-containing pituitary tumors as well as thyroid neoplasia have been produced in rats by both I^{131} and thiourea derivatives.† Maloof [47] was able to inhibit the development of pituitary tumors as well as prevent the histologic changes in the thyroid gland by the administration of desiccated thyroid. Doniach ‡ found a higher incidence of thyroid malignancy in rats treated concommitantly with I^{131} and methylthiouracil. These studies suggest that the development of thyroid tumors in the animals studied may have been due to excessive thyrotropic hormone. In man thyroid hormone has been used effectively to inhibit the production of this hormone and to produce involution of goiters.§

That genetic factors are important in the susceptibility to thyroid neoplasia is indicated by a comparison of the studies of Goldberg and Chaikoff,[51] who induced malignancy in 7 of 25 rats with I^{131}, with those of Maloof,[52] who under similar conditions found only 1 adenoma in 500 rats of a different strain.

In order to evaluate the susceptibility of the human thyroid gland to radiation, Quimby and Werner [53] questioned 101 radiologists and thyroid specialists as to the occurrence of thyroid malignancy in patients who had received x-ray therapy to the cervical region. They concluded that there was no evidence of increased rate of neoplasia. Soley and Stone [37] in a review of 48 cases of thyrotoxicosis treated with x-ray were unable to find any evidence of thyroid malignancy. However, Simpson [54] and Clark [55] suggested that thymus irradiation in infancy may result in thyroid malignancy. Radioactive iodine has been found to cause pleomorphic changes of cell nuclei in the human thyroid gland,‖ but after more than 14 years of experience no cases of thyroid malignancy due to radioactive iodine have been reported.

† References 44-46.

‡ References 48 and 49.

§ Reference 50 and Crile, G., Jr.: Personal communication to the authors.

‖ References 56 and 57.

The incidence of thyroid malignancy in association with or following thyrotoxicosis is small, Werner [58] estimating this to be in the neighborhood of 0.1%. Although no cases have as yet been reported, it appears inevitable that thyroid malignancy will be found in patients who have received radioactive iodine. If the incidence is not appreciably greater than in those treated with other methods, radioactive iodine cannot be incriminated as being carcinogenic in man.

(*b*) The potential genetic hazard of radiation from I^{131} is unknown in our present state of knowledge. The genetic effect of tremendous radiation from nuclear weapons is still questionable, and there is wide disparity of opinion amongst geneticists themselves. Consequently, it is impossible to assess the effect of the comparatively minute amounts of radiation from therapeutic doses of I^{131}. The uptake of I^{131} in various human tissues after massive doses given for thyroid carcinoma has been assessed in 13 patients by Kurland and Freedberg.[59] The gonads were found to contain only minute amounts of radiation, less than many other tissues. It thus seems unlikely that an appreciable hereditary effect would occur. However, it is probably not advisable to administer I^{131} to pregnant women, in view of possible effects on the more susceptible developing fetus or on fetal thyroid tissue.

SELECTION OF THERAPY IN THYROTOXICOSIS (TABLE 2)

The selection of treatment in any individual case of thyrotoxicosis depends on the type of disease present, the age of the patient, consideration of the patient's general physical status, and the availability of different forms of therapy.

In diffuse toxic goiter, radioactive iodine is the preferable form of treatment in most cases. The morbidity inherent in surgery is avoided, and the cost to the patient is usually less. Hospitalization, if necessary, is brief. Exophthalmos, when present, is probably less apt to be aggravated following radioactive iodine. Formerly, because of the theoretical possibility of producing thyroid malig-

nancy, the trend was to avoid using radioactive iodine in patients under the age of 40. However, as more experience has been accumulated, we do not hesitate to treat younger patients, particularly patients with associated medical disorders or who refuse surgery, believing that we are substituting a slight potential hazard for a definite immediate surgical morbidity. Pregnant patients are treated with antithyroid drugs and desiccated thyroid until after the postpartum stage. Prepubertal children and adolescents are best treated by subtotal thyroidectomy.

In toxic nodular goiter selection of treatment has most frequently been subtotal thyroidectomy, but in the majority of cases treated with radioactive iodine the response has been satisfactory. If other disease which might increase the surgical morbidity is present radioactive iodine is the preferable form of treatment. Radioactive iodine is a satisfactory means of preparing patients for thyroidectomy, and in several cases where this was intended it was found that surgery was no longer necessary. Solitary toxic nodules are particularly apt to respond well. We have reached the conclusion that surgery is absolutely indicated only in those cases where the goiter is unusually large or where mechanical difficulties are present.

In recurrent thyrotoxicosis following subtotal thyroidectomy radioactive iodine is the treatment of choice, as it avoids the increased technical difficulties of reoperation with the associated increased morbidity.

SUMMARY AND CONCLUSIONS

The current methods of therapy of thyrotoxicosis are reviewed.

Our experiences with I^{131} in the treatment of 132 patients with thyrotoxicosis and nonthyroid cardiac disease are presented.

Radioactive iodine is the preferable type of therapy in diffuse toxic goiter because (*a*) surgical morbidity is avoided, (*b*) the theoretical possibility of thyroid malignancy occurring from radioactive iodine is unlikely, and (*c*) results of treatment with radioactive iodine are equally as good, if not better, as with the use of surgery.

Toxic nodular goiter may be satisfactorily treated with either radioactive iodine or subtotal thyroidectomy. Surgical treatment is specifically indicated in those cases in which the goiter is unusually large or where mechanical difficulties are present.

Radioactive iodine may be satisfactorily used as preparation for surgery in cases of toxic nodular goiter.

Recurrent toxic goiter is best treated with radioactive iodine because of the increased morbidity if reoperation is attempted.

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TABLE 2.—*Surgery Versus I^{131} in the Treatment of Thyrotoxicosis*

	Per Cent of Patients	
Complications	Surgery	I^{131}
Mortality	0.1 to 1	None reported
Recurrent laryngeal nerve damage	0.45 to 5.25	None reported
Hypoparathyroidism	0.2 to 5.0	Theoretical
Hypothyroidism	4.5 to 29.7	8.0 to 17.2
Recurrence	1.0 to 6.85	Rare
Thyroid malignancy	None	Theoretical

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Progress in Internal Medicine

MITRAL STENOSIS

Clinical Diagnosis, Treatment, and Follow-Up of a Select Group

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DEVELOPMENT of successful surgical techniques for the relief of mitral stenosis * has made necessary the careful evaluation of patients who might benefit from mitral surgery. Numerous papers have appeared in the literature which describe the indications for surgical intervention and various methods which may be used to establish the presence of relatively "pure" mitral stenosis.† As a result of our experience with approximately 500 patients subjected to mitral commissurotomy, we have come to rely most heavily upon a detailed and complete history and a thorough physical examination, with emphasis on careful cardiac scrutiny. In addition, we have found the following helpful: fluoroscopic and orthocardiographic studies employing barium as a contrast medium (posteroanterior view and both oblique views); the standard 12-lead electrocardiogram; usual laboratory studies, such as differential blood cell count, urinalysis, and sedimentation rate, and other procedures specifically indicated.

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* References 1-3.

† References 4-8.

This study is a clinical analysis of 67 consecutive patients who were admitted to a private hospital with the provisional diagnosis of predominant mitral stenosis suitable for surgical correction. These patients were selected from approximately four times that number who were referred to us as possible candidates for mitral valvulotomy: the others were deemed unsuitable because of associated valvular lesions, irreversible pulmonary insufficiency or myocardial insufficiency, or because effects of the stenosis were not sufficiently pronounced to warrant surgery.

PURPOSE OF STUDY

This paper has been prepared with several purposes in mind: First, we wish to demonstrate the degree of accuracy with which the average internist should be able to diagnose surgically correctable mitral stenosis using only simple and readily available diagnostic tools. Second, we should like to present a few hints as to preoperative and postoperative management. Third, we propose to assess the one- and two-year follow-up results in patients typical of those commonly seen in private practice.

THE PATIENTS STUDIED

Age and Sex

The group included 56 women (84%), averaging 38.5 years of age, and 11 men (16%), with an average age of 39.0 years. The youngest was 26 years of age; the oldest, 59.

Our experience confirms the impression of other investigators that age is not per se a contraindication to surgery.[9] Nevertheless, factors such as irreversible pulmonary changes, myocardial insufficiency, associated coronary artery disease, or marked calcification of the valve—all obstacles to successful surgery—are met with most frequently

among older persons. Our oldest patient, a man 59 years of age, died during surgery because of far-advanced pulmonary emphysema, pulmonary fibrosis, and coronary artery disease. A complete summary of his case (Case 6) is included in this paper.

History of Rheumatic Fever, Tonsillitis, or Scarlet Fever

Thirty-five patients (52%) had a definite history of rheumatic fever. Another seven patients gave a history of probable rheumatic fever: in these cases, however, the evidence was inconclusive. Incidences ranging from 50% to 70% have been reported by other investigators.‡

Sixteen patients gave a past history of scarlet fever, and thirteen patients stated that they were subject to an excessive number of sore throats and tonsillitis.

Fifteen patients (22%) gave no past history of any of the aforementioned diseases.

Family History of Rheumatic Fever

Eleven patients (17%) gave a family history of rheumatic fever. We believe that exposure to a Streptococcus carrier in the home is the most tenable explanation. Recent reports as to the efficacy of penicillin used prophylactically and the high incidence of rheumatic fever associated with scarlet fever and recurrent respiratory infections lend support to this view.§ Possibly there is a hereditary factor: Wilson [15] has reported that 40 of 121 children from genetically susceptible families developed rheumatic fever.

Subacute Bacterial Endocarditis

Six of our patients (9%) reported treatment for subacute bacterial endocarditis at some previous time. In each instance the infection had occurred since adequate chemotherapeutic measures have become available.

In our opinion, at least six months should elapse between eradication of subacute bacterial endocarditis and subsequent mitral surgery. The six-month interval was decided upon empirically; we know of no evidence in support of either a longer or a shorter period of observation. None of our patients developed subacute bacterial endocarditis during surgery or the follow-up period.

‡ References 10 and 11.

§ References 12-14.

Embolic Phenomena

Sixteen patients (24%) reported embolic episodes in the past: of these, nine had suffered single episodes; five, two episodes, and two patients, three episodes—twenty-five in all. Their distribution was as follows: 14 cerebral, 1 pulmonary, and 10 in the extremities or in abdominal organs.

PROCEDURE FOLLOWED

Preoperative Procedure.—All patients were admitted to the hospital approximately five days prior to surgery. During their hospital stay, management was a joint venture between the medical and surgical groups. Disturbances in cardiac rate, fluid retention, electrolyte balance, or associated medical abnormalities were corrected insofar as possible.

In order to insure complete coverage of all important facts, not one but three complete histories were taken by different observers on separate occasions, and each patient was given three physical examinations. The combined findings were then evaluated carefully by the entire medical team: Each patient was classified according to the functional and therapeutic classification of the American Heart Association. Special attention was paid to presenting symptoms; to past history, especially to episodes of rheumatic fever, subacute bacterial endocarditis, and embolic phenomena, and to family history.

Full fluoroscopic and orthocardiographic studies of each patient were prepared by the same radiologist and reviewed by both surgical and medical teams. Barium was employed as a contrast medium in these studies, and posteroanterior and both oblique views were obtained. Twelve-lead electrocardiograms were obtained for each patient. Laboratory studies routinely requested include differential blood cell count, hematocrit determination, urinalysis, sedimentation rate,

blood urea nitrogen in the fasting patient, and prothrombin time.

We asked for cardiac catheterization of four patients because their symptoms suggested possible coexistence of interatrial septal defects. In four other patients associated pulmonary pathology, presumably secondary to long-standing mitral stenosis, was evaluated in complete pulmonary-function studies.

At Operation.—Heart action was monitored by a continuous electrocardiogram. The same anesthetist was present in each case studied. Endotracheal anesthesia with nitrous oxide, oxygen, and ether was used in each instance. All operative findings were recorded in detail by the surgeon, and degree of regurgitation felt by the exploring finger before and after valvulotomy was noted. Use of finger-fracture and/or the Bailey knife was determined by the operative findings.

Postoperative Procedure.—All patients were seen a minimum of twice a day by the medical team; ventricular rate was carefully controlled, and painstaking attention was given to change in murmurs, development of friction rub, tracheal suction, and onset of signs and symptoms of "postcommissurotomy syndrome."

Patients in the study have been followed postoperatively for periods of 12 to 24 months. The six patients who died within that period were autopsied.

This paper is concerned primarily with the clinical aspects of cases under study. Several cases are presented in detail.

SYMPTOMS

We are agreed with other observers that a number of patients may—with adequate observation and proper medical management—live for many years in relative comfort, experiencing little distress except after unusual exertion. A few may even live out a relatively normal life span with little or no restriction in normal activity.‖ Before surgical enlargement of a stenosed mitral valve is recommended, the stenosis must have progressed to a point where it handicaps the patient; observation over a reasonable period must have demonstrated that, despite optimal medical management, the patient's condition is describing a downward course, and surgery must offer the hope of improvement in the patient's condition or, at the minimum, halt the downward course of the disease.

Sixty-three of the sixty-seven patients under study (94%) complained of progressive dyspnea. In many patients dyspnea was present only on exertion; in approximately 15% dyspnea was also present during rest. Paroxysmal dyspnea occurred in most of our patients at some time during their illness: the occasions usually were associated with some exciting factor such as pregnancy, previous surgery, or severe infection. Lewis and others ¶ have postulated that the bouts of paroxysmal dyspnea represent repeated episodes of left atrial failure secondary to mitral stenosis in patients in whom a protective rise in pulmonary vascular resistance had not yet developed.

Fatigue was a principal complaint in 29 patients (43%), many of whom stated they were not as disturbed by exertional dyspnea as by a constant feeling of weakness. Initially, we believed that the fatigue was of neurogenic origin, but fatigue was reported with such regularity that we have accepted it as an important symptom and are now of the opinion that in severe mitral stenosis fatigue is in some manner directly related to the reduction in cardiac output.

Hemoptysis was equally as common as fatigue, also being present in 29 patients (43%). When we speak of hemoptysis, we refer to definite spitting of blood and not to the frothy pink sputum commonly associated with pulmonary edema. Our figure compares favorably with the 47% reported by Logan and Turner.[20]

Recurrent pneumonia was reported by 21 patients (31%). Many other patients reported attacks of acute bronchitis and so-called "asthmatic bronchitis." Several patients were treated for years as typical

‖ References 16 and 17.

¶ References 18 and 19.

asthmatics until the diagnosis of mitral stenosis was established.

Other commonly reported symptoms are palpitation, irregular heart action, tachycardia, ankle edema, angina-like pain, and syncopal attacks. Initially, we had thought that the repeated syncopal attacks might be correlated with ball-valve thrombus of the mitral valve; in no case were we able to demonstrate such a relationship. Attacks of syncope are most logically explained as due to reduced cardiac output with cerebral anoxia, tachycardia, or vasovagal episodes.

CARDIAC ENLARGEMENT

In addition to physical examination the Ungerleider-Clark [21] tables were used to evaluate the degree of enlargement evidenced in the x-rays. A valuable physical sign which correlated well with other evidence of right ventricular hypertrophy was lift of the lower left parasternal area,[22] noted in 33 patients (50%).

TABLE 1.—*Cardiac Enlargement*

Degree of Enlargement	Patients	
	No.	Per Cent
None	5	7
+1	7	10
+2	36	54
+3	15	23
+4	4	6

Degrees of cardiac enlargement found are summarized in Table 1.

APICAL DIASTOLIC THRILL

An apical diastolic thrill was noted in 36 patients (54%). In several patients this thrill was well localized and became evident only after mild exercise.

AUSCULTATORY FINDINGS

In every instance the pulmonic second sound was accentuated; in 25 patients (37%) the sound was split. Harvey and his coworkers [23] recently have emphasized the importance of demonstrating significant active pulmonary artery pressure elevation if we are to relate the patient's symptoms to mitral block rather than to myocardial insufficiency. Although a loud P_2 is commonly seen in left atrial or left ventricular failure and is generally accepted as evidence of increased pressure within the pulmonary circuit, we caution against using this one finding alone as evidence of active pulmonary hypertension. In our own study we found poor correlation between the degree of hypertension and loudness of the P_2, and experience has demonstrated that equivocal results are obtained in mitral commissurotomy if pulmonary artery pressure is normal or only slightly elevated.

A Graham Steell murmur was present in 24 cases (36%). This typical decrescendo murmur along the left sternal border usually indicates a severe degree of pulmonary hypertension and/or dilation of the pulmonary valve ring. Although many standard textbooks indicate that a Graham Steell murmur is only an occasional finding, our experience indicates that this murmur is a frequent finding in patients with far-advanced mitral stenosis. Difficulty may be encountered in differentiating a murmur of pulmonary insufficiency from one of aortic insufficiency, but when the murmur is considered against the total hemodynamic background and in connection with the entire clinical picture the source of the murmur is readily apparent.

In every case subjected to surgery, we were able to elicit the characteristic diastolic murmur of mitral stenosis at the apex, although on occasion this murmur became audible only after exercise and even so was localized to a small area just inside the site of the apical impulse. The first sound invariably was snapping. Systole was extremely short, with prolongation of the ventricular diastolic filling period. Commonly, a mitral opening snap was heard at the fourth interspace along the left sternal border.

Twenty-six of our patients (39%) had systolic murmurs readily heard at the apex. In most instances these murmurs were Grade 1 or Grade 2 in intensity and, when transmitted, were heard at the left sternal border. In correlation of physical findings with other diagnostic modalities, these murmurs did not appear to be physiologically significant;

they probably represented changes such as shortening of the chordae tendinae or slight tricuspid insufficiency or were caused by calcification of the median leaflet of the mitral valve. Four patients had apical systolic murmurs of Grade 3 intensity, with transmission toward the axilla: In three instances these murmurs were thought to indicate mitral insufficiency subordinate to the dynamically more important stenotic lesion; in the fourth, catheterization disclosed the typical pattern of tricuspid insufficiency and once the patient had been fully compensated prior to surgery the murmur was no longer audible.

Three patients had Grade 2 systolic murmurs at the primary aortic area, with transmission to the neck vessels. None of the three had associated peripheral evidence of aortic stenosis. Two of the three patients had been considered for mitral commissurotomy a year previously but had been rejected at that time because of the associated aortic murmurs. Because their conditions continued to deteriorate under medical management alone (confirmed in one patient by cardiac catheterization), these patients finally were accepted for surgery, albeit reluctantly. Unfortunately, one of the two patients died and the other obtained a poor result (Cases 3 and 4). We are convinced that—unless one is prepared to operate on both the mitral and aortic valves—patients with both mitral and aortic stenosis do better without surgery on the mitral valve alone.

RADIOGRAPHIC FINDINGS

Significant selective enlargement of the left atrium was noted in the right anterior oblique projections of all patients. Pastor [24] has described the use of body-section radiography as helpful in demonstrating the enlarged left atrium in cases in which conventional films fail to bring out this feature properly, but we feel that this rarely is indicated in the cardiac assessment of the average candidate for mitral commissurotomy.

In 65 of our patients (97%) the posteroanterior cardiac silhouette showed the typical mitral configuration.

At fluoroscopy an attempt was made to note calcium within the valves. Since calcium can be spotted more easily in these than in routine x-rays, films were obtained in the posteroanterior projection and in both oblique views, with use of barium as a contrast medium. Recently we have begun to use 7 ft. Bucky films obtained in the posteroanterior projection, to demonstrate calcium in the several valve areas better and to delineate with greater clarity the double-contour shadow so often seen in mitral stenosis.

Radiographic evidence of calcium in the mitral valve was noted in 10 instances; in each, this was confirmed at surgery. However, calcium which had not been noted in films or on fluoroscopic examination was found at surgery in nine additional mitral valves. (Total number of patients with calcified mitral valves was 19 [28%].)

Bronchial-vascular markings were moderately to markedly increased in the lung fields of 30 patients (45%). Many of these patients showed ground-glass haziness throughout both lung fields indicative of extensive hemosiderosis.

Radiograms of one patient, a 59-year-old man, suggested far-advanced pulmonary emphysema, later confirmed by complete pulmonary-function studies (Case 6). Bronchographic studies taken at an earlier date showed a second patient to have bilateral bronchiectasis, and serial films of a third patient—together with his clinical history—supported a diagnosis of recent pulmonary infarction.

We were unable to differentiate satisfactorily between right and left ventricular enlargement on the basis of generally accepted criteria.# (Sussman and Jacobson [27] experienced similar difficulty when studying other conditions causing right ventricular hypertrophy.) For example, in seven cases in which the radiological impression suggested left ventricular enlargement, the electrocardiogram showed no evidence of significant left ventricular hypertrophy. At operation, six

References 25 and 26.

of the seven were found to be cases of relatively pure mitral stenosis; the seventh, an instance of tight mitral stenosis with estimated +1 regurgitation. Again, in four patients in whom +2 regurgitation was found at surgery the orthocardiogram showed no appreciable left ventricular enlargement, and an electrocardiogram detected ventricular enlargement in only one of the four (Case 4).

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram proved to be one of the best aids in confirming the diagnosis of pure mitral stenosis. Routinely the standard 12-lead electrocardiogram was used, and in all but a few instances an additional V_3R lead was obtained. Usually, previous tracings were available for comparison. The criteria proposed by Sokolow and Lyon * were used to determine right and left hypertrophy.

Electrocardiographic evidence of right ventricular hypertrophy was found in 32 patients (48%). Abnormal P waves (P mitrale) or atrial fibrillation associated with right axis deviation and a vertical heart were found in 34 patients (51%). Evidence of left hypertrophy was present in two patients: This condition was confirmed at surgery in one patient; the other had pure mitral stenosis.

Preoperatively 38 patients (57%) had atrial fibrillation; 29 (43%) had normal sinus rhythm. We did not attempt to convert atrial fibrillation to a normal sinus mechanism. After surgery, all patients who previously had demonstrated atrial fibrillation maintained the fibrillation, and 10 patients with normal sinus rhythm preoperatively developed atrial fibrillation.

Five of our patients (7%) had normal tracings: Four of these were found to have pure mitral stenosis at surgery; the surgeon reported no significant mitral stenosis in the fifth, who earlier had undergone cardiac catheterization without demonstration of an intracardiac shunt. This case has been reported previously † as one of a group with false mitral stenosis, and is presented in detail in this paper (Case 2).

One patient had electrocardiographic evidence of myocardial ischemia (Case 6).

FUNCTIONAL CLASSIFICATION

None of the patients was in Class I. Seven (10%) were in Class II; fifty (75%) were in Class III, and ten (15%) were in Class IV.

PREOPERATIVE DIAGNOSES

Our preoperative diagnoses in these 67 cases were as follows: pure mitral stenosis, 61; predominant mitral stenosis and associated mitral insufficiency, 3; predominant mitral stenosis and associated aortic stenosis, 3.

INCIDENTAL PROCEDURES

Prior to hospital admission, seven patients received bishydroxycoumarin (Dicumarol) as a protection against recurrence of embolic phenomena; their prothrombin levels had been kept at 40% to 50% of normal. Bishydroxycoumarin therapy was discontinued during the preoperative period, without incident.

None of the patients demonstrated either clinical or laboratory evidence of rheumatic activity.

THROMBI WITHIN THE LEFT ATRIUM

Basing our decisions upon the previous occurrence of embolic episodes, atrial fibrillation, and syncopal attacks, we attempted to establish preoperatively whether or not a thrombus was present within the left atrium. Eight times the diagnosis was made; we were wrong in each instance. Apparently patients who have had previous embolic episodes are no more likely to have a thrombus within the atrium than patients who have never suffered embolism. Ten patients (15%) were found at surgery to have thrombi within the left atrium; these thrombi were undiag-

* References 28 and 29.

† Mahoney, D.: Mitral Commissurotomy for False Mitral Stenosis, read before the 24th Annual Symposium of the Los Angeles County Heart Association, Oct. 14, 1954.

nosed clinically. Apparently thrombi within the left atrium are difficult to diagnose short of actual exploration of the atrium: Unless one also plans to correct coexisting mitral stenosis in the same operation, we are convinced of the futility of surgery for the sole purpose of removing a clot from the atrium. Too, fresh thrombi and not old organized clots are the source of emboli.

CORRELATION OF CLINICAL DIAGNOSIS WITH SURGICAL FINDINGS

The diagnosis of pure mitral stenosis was made in 61 cases. Of the other six, three patients were believed to have a minimal degree of mitral insufficiency, and three others, coexisting aortic stenosis. Nevertheless, mitral stenosis was considered to be the primary valvular difficulty.

At surgery, 60 patients were found to have mitral orifices estimated to be 1 sq. cm. or smaller; 53 of these patients had pure mitral stenosis; in another 7 the regurgitant jet was estimated by the surgeon to be minimal to +1.

In four patients the degree of mitral regurgitation was judged to be +2; in two of these the orifice exceeded 1 sq. cm. but a significant degree of stenosis was present. We had been prepared to find mitral insufficiency in two of the four.

A third case in which associated mitral insufficiency was suspected was found at operation to be pure mitral stenosis.

Coexistent aortic stenosis was diagnosed in three patients, one of whom also had associated mitral insufficiency. As previously mentioned, two of these patients had initially been refused surgery because of the aortic involvement. The aortic lesions were confirmed at surgery in these two patients; the third patient was found to have pure mitral stenosis.

Because of their unusual nature, the final two cases are presented in detail. One had a fibrocalcific band in the region of the atrioventricular groove, probably of tuberculous origin, which constricted the mitral opening, simulating mitral stenosis (Case 1). The remaining patient was found at surgery to have no mitral lesion (Case 2).

Clinical impressions were confirmed at surgery in the majority of cases. Janton and his co-workers,[30] reviewing 247 cases subjected to mitral commissurotomy, reported similar correspondence between clinical impression and findings at surgery.

IMMEDIATE POSTOPERATIVE FINDINGS

The operating surgeon estimated the degree of regurgitation in each patient both preoperatively and postoperatively. Seventeen patients in whom no regurgitation existed prior to valvulotomy developed +1 regurgitation; in three the degree of regurgitation increased from 0 to +2 following operation; in two others it rose from a preoperative + 1 to a postoperative + 2. Of course the full significance of these findings will not become apparent until a far greater number of cases have come under scrutiny over a much longer postoperative period. We have noted with interest that, of the 22 cases in which regurgitation was increased following valvulotomy, a knife was used in 18. The method of performing valvulotomy described by Beck [31] may be helpful in preventing the development of regurgitation postoperatively.

Postoperative and preoperative auscultatory findings were correlated as follows: Preoperatively, 26 patients had apical systolic murmurs; in 23 of them, intensity of the murmurs was either Grade 1 or Grade 2; in three, the murmur was Grade 3 in intensity. Postoperatively, the number of patients with apical systolic murmur had risen to 35; in 11 patients the murmur was of the magnitude of Grade 3 or Grade 4, although 8 of the 11 patients in this group had either no murmur or only a Grade 1 murmur preoperatively. Again, we note that a knife was used to perform the commissurotomy in 10 of the 11 patients.

A pericardial friction rub was audible at some time during convalescence in 28 of the 61 patients surviving the operation (46%). Probably a friction rub would have been heard in every case if surgical dressings had

not interfered with proper auscultation during the period when a rub would have been most audible.

CLINICAL MANAGEMENT

Preoperative Period.—Our patients were hospitalized approximately five days prior to operation. In order to insure adequate control of the ventricular rate during surgery, each patient received digitalis preparations during his hospital stay. Because of its low toxicity ‡ gitalin (Gitaligin) is the preparation we prefer; in most instances 1.5 mg. daily, administered in divided doses, proved ample. In no instance were we able to demonstrate toxic symptoms attributable to the digitalis per se either in the preoperative or in the postoperative period.

Ancillary measures included the prophylactic administration of penicillin, restriction of daily sodium intake to 200 mg., and—if indicated—use of mercurial diuretics. Quinidine was not employed preoperatively because of its depressant effect on the myocardium.

At Operation.—Premedication was prescribed by the anesthetist, who saw the patient the day before surgery. During surgery every case was monitored with the aid of a continuous-writing electrocardiograph and oscilloscope; cardiac drugs were used but rarely, and only upon the advice of the cardiologist. Adequate tidal exchange proved the most useful single measure to combat arrhythmias, hypotension, and tachycardia during surgery. Drugs most commonly employed were atropine and methoxamine. Blood was used for replacement of estimated loss.

Postoperative Period.—For two or three days following surgery all patients were attended by nurses especially trained in the handling of chest cases.

Maintenance of an adequate airway by prompt and thorough tracheal toilet is of utmost importance and, in one instance, proved life-saving. Cough was encouraged, and penicillin prophylaxis was employed. Oxygen was supplied by nasal catheter or intermittent positive pressure. Measures were taken to prevent cardiac failure, and excess fluid was removed by thoracentesis when indicated. Careful records of intake and output were kept.

Dietary sodium restrictions were removed during the first three days after surgery. Early in our series, before this precautionary measure was adopted, low-salt syndrome developed in one patient. Persons usually come to operation after prolonged periods of salt restriction, with serum sodium values approaching the lower limits of normal. During surgery and in the immediate postoperative period, these patients lose excessive amounts of NaCl via the skin; at the same time reduced output of urine and the administration of salt-free fluids tends to dilute stores of sodium already perilously low. As Goodyer and Glenn [35] have demonstrated in their studies of electrolyte balance, hyponatremia is a definite entity in patients undergoing mitral valvulotomy.

Depressant drugs such as morphine and meperidine (Demerol) were used infrequently; as soon as feasible, pain was controlled by codeine and acetylsalicylic acid. Lanatoside C (Cedilanid) was given intravenously to control rapid supraventricular rate. In retrospect, we feel certain that several of our patients had episodes of rapid supraventricular response after receiving meperidine. This drug reaction has since been described by other investigators,[36] but at the time we were unaware of the phenomenon.

Corticotropin and cortisone were employed in only a few instances in which the possibility of rheumatic reactivation occurred.

Gitalin was employed when indicated; the low toxicity of this digitalis preparation was especially gratifying in postoperative management.

Upon discharge, all patients received instruction as to activities and continuation of salt-poor diet and digitalis, and they were requested to return for periodic checks. Daily dose of oral anticoagulant was continued for some patients. Several of the younger pa-

‡ References 32-34.

tients, and patients whose rheumatic fever had been reactivated, were placed on long-term oral penicillin prophylaxis.

At least six months and preferably one year was permitted to elapse following surgery before conversion of atrial fibrillation to normal sinus rhythm was attempted, as we felt that the traumatized atrium would be stubbornly resistant to conversion. When deemed advisable, conversion was always attempted in the hospital under electrocardiographic control, and the patient was given anticoagulants.

EMBOLI AT SURGERY OR POSTOPERATIVELY

No fatal embolic episodes occurred in this series. One patient developed right hemiplegia during surgery, which responded to treatment with stellate ganglion block followed by intravenously administered hydrogenated ergot alkaloids (Hydergin) and heparin. At the time she was discharged from the hospital, power had partially returned to the involved limbs and the patient's speech had improved. Her condition has continued to improve since her discharge.

A second patient, who, prior to surgery, had had a pulmonary embolus, suffered a fresh embolus to her right leg on the second postoperative day. She made an excellent recovery after anticoagulant therapy and was counseled to continue taking bishydroxycoumarin.

No embolic episodes were recognized in the remainder of the patients during their hospital stay; none of patients has suffered an embolism or has developed subacute bacterial endocarditis during the follow-up period.

RHEUMATIC ACTIVITY IN THE AURICULAR APPENDAGE

Auricular appendages were examined in 65 cases; 20 (31%) were positive for rheumatic activity. In 16 of the 20 cases the patients had had normal sinus rhythm prior to surgery, an incidence of 80%. Seventeen of the twenty appendages showing rheumatic activity had come from persons under 40 years of age. Thus our findings are in keeping with earlier reports § that rheumatic activity is found in approximately 35% of the appendages studied and that rheumatic involvement is most common in persons under the age of 40 who have normal sinus rhythm.

POSTCOMMISSUROTOMY SYNDROME

Fourteen of the sixty-four patients who survived the operation (22%) developed symptoms of postcommissurotomy syndrome during their hospital stay. A similar incidence has been reported by Soloff,[39] Ellis,[40] and Jones.[41]

One patient became acutely psychotic but made a complete recovery. Another developed fulminating rheumatic pneumonitis, to which she succumbed (Case 5).

Apparently, penicillin failed to forestall development of the syndrome. In most instances, salicylates exerted a beneficial effect.

REPORT OF CASES

CASE 1.—A 26-year-old white man was admitted to the Good Samaritan Hospital in April, 1954, for mitral surgery. Cardiac enlargement had first been noted in October, 1950, from which time the patient reported progressive dyspnea and edema, both of which had become marked in the past seven months. Treatment had consisted of low-salt diet, digitalis, and periodic injection of meralluride (Mercuhydrin) to control the failure. Past history and family history were noncontributory.

Physical examination revealed a well-developed well-nourished man in moderate distress. Neck veins were distended, and pulsations representing A and V waves were present. Blood pressure was 120/70 in both arms. The margin of the liver was palpable 2 fingerbreadths below the costal cage and was very tender. The lungs were clear. The heart was enlarged, with the left border of dullness 2 cm. to the left of the midclavicular line. No point of maximal impulse was felt. No thrills or thrusts were palpable. The rhythm was totally irregular, at an apical rate of 80. Heart tones were heard at all the valve areas, with M_1 accentuated, and P_2 was greater than A_2. A low-pitched diastolic rumbling murmur was audible at the apex.

Orthocardiograms in the right anterior-oblique projection revealed a mitral type of configuration, with a prominent pulmonary artery segment, a double-contour shadow, and enlargement of the left atrium. No calcium was noted. The lungs were clear.

§ References 37 and 38.

An electrocardiogram revealed atrial fibrillation, right-axis deviation, and right ventricular hypertrophy. Because of sharply inverted T waves in the left precordial leads, local myocardial disease was suspected.

The clinical impression was that of pure mitral stenosis with progressive symptoms despite adequate medical management. The patient was treated in the usual fashion, with good clearing of the failure, and at the time of surgery was classified Grade II-C.

Surgery was done on April 16, 1954, through a left thoracotomy. The pericardial sac was found to be obliterated, and the pericardium was thickened. In the region of the left atrium several thick plaques of pericardium were noted, closely adherent to the epicardium in the region of the A-V sulcus; these were dissected free and removed. Pulmonary artery pressure was felt to be elevated minimally. Exploration of the left atrium revealed a normal mitral valve and an intact interatrial septum. The final surgical impression was calcific pericarditis with localized constriction in the region of the A-V sulcus.

The patient made an uneventful recovery and was discharged into the care of his local physicians, with good relief of all symptoms.

Comment.—This is a case of false "mitral stenosis" which had the physical, radiographic, and electrocardiographic appearance of mitral stenosis of valvular origin, yet was actually caused by an external constriction in the region of the A-V sulcus. Edwards [42] recently has presented an excellent clinicopathologic review of conditions simulating mitral stenosis. In our experience, atrial septal defect has been the commonest cause of false "mitral stenosis," and the simultaneous presence of interauricular septal defect and mitral stenosis (Lutembacher's syndrome) is extremely rare.

CASE 2.—A 26-year-old woman was admitted to the Good Samaritan Hospital in October, 1953, with a chief complaint of progressive fatigue and dyspnea on exertion. As a child, she had suffered many joint pains and "growing pains," associated with dyspnea. In July, 1952, the patient had developed hemiplegia of the left side, which apparently had been caused by mycotic embolization and which cleared with good recovery of motor function once the underlying subacute bacterial endocarditis had been eradicated by a six-week course of antibiotic therapy.

Physical examination revealed a well-developed well-nourished normotensive white woman in no acute distress. Pertinent findings were confined to the heart, which appeared normal in size. A lift was felt in the region of the third and fourth intercostal space to the left of the parasternal line. A pulmonary closure tap was present, and at the mitral area a light diastolic thrill ending with a tap was noted. Heart tones were heard clearly at all valve areas. P_2 was more pronounced than A_2 and was split; the first sound at the apex was greatly accentuated. At the apex a mid- and late-diastolic crescendo murmur was heard, with marked shortening of the systolic period. A very short systolic murmur also was audible.

Orthocardiograms in the right anterior-oblique projection revealed only minimal enlargement of the left atrium. An electrocardiogram showed normal sinus rhythm with a normal axis and R-R' wave in the right precordial leads.

The clinical impression was pure mitral stenosis secondary to rheumatic fever; the patient was judged to be in Class II-C.

During exploratory surgery a normal-appearing heart and mitral valve were found. In the opinion of the surgeon, pulmonary artery pressure was not elevated. No clots or calcium were present within the valve or the atrium. After the patient's uneventful recovery from surgery, pressures and oxygen samples were obtained from the right side of the heart and from the pulmonary artery by cardiac catheterization. Pressures were all within normal limits, and no shunt was demonstrated.

Comment.—This patient has been followed on an outpatient basis since surgery. Her physical findings and symptoms remain unchanged. We have no adequate explanation as to the cause of the symptoms or the physical findings.

CASE 3.—A 47-year-old white woman was first seen in September, 1952, with chief complaints of exertional dyspnea, easy fatigue, and palpitation. At the age of 17 the patient had been told that she had a heart murmur, but no past history of rheumatic fever was noted. Despite adequate medical measures the patient's symptoms had become progressively worse during the previous five years.

Examination revealed significant findings to be confined to the heart. Cardiac enlargement was Grade IV, and a lift was present in the parasternal area. No thrills or taps were felt. Heart tones were heard clearly at all valve areas. P_2 was greatly accentuated and closely split. M_1 was accentuated. A loud, blowing Grade 3 systolic murmur was heard at the base of the heart, was maximal over the pulmonic area, and was transmitted to the left axilla and under the left clavicle. The murmur was not audible in the neck vessels. At the left sternal border a diminuendo murmur was heard. At the apex a low-pitched, mid- and late-diastolic murmur could be heard, which ended with a snapping first

sound. Heart rhythm was regular; blood pressure was 115/80.

Orthocardiograms and fluoroscopic studies revealed very marked prominence of the pulmonary artery segment and accentuation of the hilar vessels. The heart was enlarged, and, in the right anterior-oblique projection, decided enlargement of the left atrium was apparent. In the opinion of the radiologist, these findings were compatible with the clinical diagnosis of simultaneous presence of interauricular septal defect and mitral stenosis.

The electrocardiogram demonstrated large broad notched P waves in Lead II, with an associated right bundle branch block. Cardiac catheterization failed to disclose a shunt; however, the main pulmonary artery pressure was 95/45 mm. Hg and peripheral pulmonary artery pressure was approximately 35 mm. Hg. At that time surgery was not advised because of the loud basal systolic murmur.

In June, 1953, the patient was admitted to the Good Samaritan Hospital with essentially the same clinical findings as on previous examination. Although she was believed to be a poor risk, operation was advised at this time because of the progressive downhill course of her condition, despite the severe pulmonary hypertension and presence of the loud basal systolic murmur, which was believed to indicate possible aortic stenosis.

At surgery the pulmonary artery was found to be large and tense. The mitral valve was found to be calcified, and a knife was used to correct the tight mitral stenosis. Minimal mitral regurgitation was present postoperatively. A thrill was palpable over the aorta. Although blood pressure became unobtainable during surgery, the pressure returned once the mitral orifice had been widened.

Postoperatively, the urine output remained low; nonprotein nitrogen rose from 31 mg. to 108 mg. per 100 cc. Serum sodium and chlorides remained low despite corrective measures. Concomitantly, the patient developed failure of the right side of the heart and died on the 18th postoperative day.

At autopsy the heart was found to weigh 590 gm. The left atrium was dilated markedly and appeared twice the normal size. The mitral valve exhibited calcification of the superior margins; the lumen admitted a finger with difficulty, and evidence of recent surgery at the posterior commissure was present. No interatrial or interventricular defects were found. The aortic valve was calcified; the orifice was narrowed and thickening of the leaflets had occurred, and the commissures were found to have fused. Lumens of the coronary vessels were not reduced significantly, and no evidence of infarction was noted. No intracardiac clots were present. The autopsy report gives the size of the left ventricle as 18 mm. and notes that the right ventricle was hypertrophied, but no measurement is recorded.

Upon gross examination a large thrombus was found partially to occlude the lumen of the right main pulmonary artery; the lung parenchyma appeared normal. Microscopically, moderate arteriosclerosis of the lung was revealed. A recent embolus to a branch of the superior mesenteric artery had resulted in bowel infarction.

Comment.—From several standpoints, this patient was a poor candidate for surgery: Pulmonary changes were of a severe nature and probably contributed to her symptoms as fully as did the block at the mitral valve. Also, aortic stenosis was present, which we were not prepared to deal with at that time but would attack together with the mitral valve lesion if we were to operate today. Although, at the time the mitral commissurotomy was performed, we felt that the aortic lesion had minor hemodynamic significance, we are aware that an extra load was placed on an already-damaged left ventricle with the correction of the mitral lesion. Clinically, we had placed too great emphasis on the normal blood pressure and pulse pressure.

Development of a low-sodium syndrome and postoperative peripheral emboli contributed to the fatal outcome.

CASE 4.—A 37-year-old white man with chief complaints of progressive dyspnea, fatigue, and episodes of fainting was admitted to the Good Samaritan Hospital in April, 1954. He had had scarlet fever at the age of 13, and his activities had been restricted following discovery of a heart murmur. In the past, numerous episodes of heart failure had necessitated repeated hospitalization.

Cardiac findings were as follows: The heart silhouette was enlarged to the left, with the point of maximal impulse in the fifth intercostal space outside the midclavicular line. No lifts or taps were present. A diastolic thrill was noted at the apex. Heart tones were audible at all valve areas, although the first sound at the aortic area was muffled. P_2 was accentuated. An opening snap could be heard at the left sternal border, and a loud low-pitched mid- and late-diastolic murmur was noted at the apex. At the primary aortic area, a Grade 3 harsh blowing systolic murmur was heard, which was transmitted to the neck vessels. Pressure in both arms was 110/76; normal sinus rhythm was present.

Orthocardiograms revealed clear lung fields and a typical mitral configuration with a double contour; no evidence of left ventricular enlargement was present. An electrocardiogram showed notched

P waves in Leads I and II and evidence of left ventricular hypertrophy in the precordial leads.

The predominant lesion was believed to be mitral stenosis associated with a moderate degree of aortic stenosis. Because of the latter finding we hesitated to perform mitral surgery, but we finally decided upon the operation because of deterioration in the patient's status.

At surgery the pulmonary artery was large and tense. A marked thrill was felt over the aortic valve. The left atrium was free of clot, but the mitral valve was calcified and a +2 regurgitation jet was present in addition to the fairly tight mitral stenosis. The valve was fractured, without increase in the degree of regurgitation.

Postoperatively, the patient developed a loud mitral systolic blow. In addition to a loud systolic murmur in the aortic area a thrill was readily palpable at the same site.

Comment.—The situation is similar to the previous case in that we were unprepared to correct the aortic stenosis at the time of mitral surgery. Postoperatively this patient has done poorly.

CASE 5.—A 28-year-old white woman with progressive symptoms of failure with extreme dyspnea, repeated attacks of pneumonia, and fatigue despite an adequate medical regimen of four years' duration was admitted to the Good Samaritan Hospital in November, 1953. Rheumatic fever had been diagnosed at the age of 8.

Physical examination revealed slight cardiac enlargement, with the point of maximal impulse in the fifth intercostal space outside the midclavicular line. Normal sinus rhythm was present; heart rate was 60. A lift was present in the lower left sternal area. A pulmonary closure tap was felt, and at the apex a diastolic thrill was discernible. Heart tones were clearly audible at all valve areas. P_2 was accentuated, and a Graham Steell murmur was noted at the left sternal border. At the apex, a loud rumbling mid- and late-diastolic murmur with accentuated first sound was heard. Systole appeared to be very short.

Orthocardiograms disclosed a typical mitral configuration with a double contour and selective left atrial enlargement. An electrocardiogram showed normal sinus rhythm with left atrial enlargement and right ventricular hypertrophy. The clinical impression was that the patient suffered from relatively pure mitral stenosis.

At surgery the pulmonary artery was found to be large and tense. Enlargement of the left atrium was noted. The mitral orifice proved too small to admit the tip of a single finger, and a knife was used to enlarge the opening. Plus one regurgitation was present after surgery.

Following surgery, fever, chills, and dyspnea developed. Respiration became rapid, and a migrating friction rub was noted. X-ray findings compatible with bronchopneumonia were found in one lung; a few days later this area had cleared, but the condition was found to have recurred in a lobe of the opposite lung. We believe these findings to represent a reactivation of rheumatic fever, with an episode of rheumatic pneumonitis. Attempts at therapy—which included corticotropin administration—were of no avail; the patient died on the 14th postoperative day.

At autopsy, the heart was found to weigh 330 gm. All valves were normal with the exception of the mitral valve, which was fibrous and stenotic. The chordae tendinae were noted to be shortened, and the papillary muscles were hypertrophied. The posterior commissure had been cut completely. The right ventricular wall measured 6 mm.; the left ventricular wall measured 10 mm.

The pleural cavities were free of fluid. The lungs were large and extremely heavy—the right lung weighing 1000 gm. and the left lung, 800 gm. The lungs were dark red, firm, and rubbery, with several hemorrhagic areas. Lung tissue was uniformly solid—smooth and rubbery, without the granularity or friability of pneumonic consolidation. Cut surfaces were only slightly wet. Histologic study of sections from the firmer basal regions disclosed profound interstitial fibrosis: The alveoli were composed of gland-like spaces lined with cuboidal epithelium and separated by myxomatous-appearing connective tissue; proliferation of endothelial cells had obliterated the lumens of the smaller arteries and arterioles. In other sections of the lung the picture was that of acute and chronic passive hyperemia.

The final pathological impression was severe mitral stenosis with recent commissurotomy. The lungs showed acute and chronic hyperemia, with interstitial fibrosis and superimposed interstitial pneumonitis.

Comment.—In this case rheumatic pneumonitis complicated an otherwise ideal situation for mitral commissurotomy. Clinical and pathologic features resembled like cases reported in the literature.§ Often it is difficult to differentiate the pneumonic manifestations of rheumatic fever from primary atypical pneumonia or effects of multiple small pulmonary emboli. In this instance, the pathologic findings were completely in accord with the clinical diagnosis of rheumatic pneumonitis and clearly ruled out the other similar-appearing conditions.

§ References 43 and 44.

CASE 6.—A 59-year-old man was admitted to the Good Samaritan Hospital in February, 1954, for treatment. No early history suggestive of rheumatic fever was given, although a heart murmur had been discovered when the patient was 18. The patient had suffered a "heart attack" at the age of 43, from which time he had taken a daily maintenance dose of digitalis. Dyspnea at rest had been present for the previous eight years. In the five months preceding hospitalization he had been subject to attacks of paroxysmal nocturnal dyspnea. Shortly before hospitalization he had suffered an episode of substernal discomfort lasting for four hours, with pain radiating into the left arm. Remainder of the history was noncontributory.

Physical examination on the morning of admission revealed a poorly nourished white man with labored respirations while at rest. The patient appeared plethoric, and a suggestion of cyanosis could be detected. The patient was apparently using his accessory muscles of respiration, and marked retraction of the supraclavicular and suprasternal areas was noted. A moderate increase had occurred in the anterior-posterior diameter of the chest. Fine moist rales were heard at both lung bases; expiration was prolonged, with numerous expiratory wheezes.

The heart was enlarged to the left, with the point of maximal impulse in the sixth intercostal space about 1 cm. outside the midclavicular line. A parasternal thrust was present. Rhythm was that of atrial fibrillation, with well-controlled ventricular response. P_2 was greater than A_2, and heart tones were readily audible at all valve areas. At the apex a mid- and late-diastolic rumbling murmur with an accentuated first sound was heard. No peripheral signs of right heart failure were noted.

An electrocardiogram disclosed the presence of atrial fibrillation, right axis deviation, a vertical heart, and digitalis effect. Tall R waves in Leads V_3R and V_1 were interpreted as indicating right ventricular hypertrophy. No electrocardiographic evidence of either old or recent infarction was noted in this tracing or in two succeeding tracings. None of the tracings demonstrated left ventricular hypertrophy. Orthocardiograms revealed selective right ventricular and left atrial enlargement, severe hemosiderosis, and an increase in the finer lung markings. The diaphragms were flattened. Calcium was present in the wall of the left atrium, in the mitral valve, and in the main pulmonary artery.

Our clinical impression was that this man had rheumatic heart disease with pure mitral stenosis and severe pulmonary vascular changes. His condition apparently was complicated by pulmonary emphysema and fibrosis and probably by coronary artery disease. The patient's condition was classified as IV-D; he was told that complete pulmonary-function studies would be required for evaluation of his pulmonary status.

Later in the day the patient developed acute pulmonary edema and was hospitalized. He responded well to the conventional methods of therapy, and arrangements were made for study at the cardiopulmonary laboratory on March 4, 1954.

The patient's vital capacity was 2680 cc. (67.4% of predicted normal). Three-second vital capacity was 2010 cc. (50.6% of predicted normal). Maximum breathing capacity was 33.6 liters per minute (30% of predicted) and rose to 55.3 liters per minute after one intermittent-positive-pressure-breathing treatment with isoproterenol (Isuprel). Alveolar nitrogen after breathing 100% oxygen for seven minutes was 5.14%. Total lung volume was decreased slightly, and residual volume was increased. The ratio of residual air to total lung volume was 44%; ventilatory factor was 46% of predicted normal.

Resting arterial blood saturation was 88.3%; arterial CO_2 content was 52.1 vol. %, with a pH of 7.52. The hematocrit value was 45%. The arterial blood saturation rose to 96.8% on 100% oxygen, and by direct tension measurement the pCO_2 was 38 mm. Hg, with a pH of 7.48. Measurements of pulmonary ventilation at rest demonstrated a slight increase in minute ventilation, normal oxygen uptake, and a moderate decrease in the percentage of oxygen extracted from inspired air.

Ether circulation time was normal, with marked prolongation of the arm-to-tongue dehydrocholic acid (Decholin) time (32.3 seconds). Plasma volume measurements (using Evans blue [T-1824] dye) were normal.

Pulmonary-function studies revealed emphysema with associated bronchospasm and marked impairment in the ability to use the lungs as a bellows, as reflected in the low ventilation factor.[45] A marked degree of unequal alveolar aeration was also noted. Although this man had moderate pulmonary disease secondary to pulmonary emphysema, bronchospasm, and fibrosis, the primary difficulty was believed to be due to the block at the mitral valve.

Intermittent-positive-pressure therapy was continued, along with adjunctive measures, and surgery was performed on March 18, 1954. At surgery the lungs were found to be fibrotic and hemosiderotic; they deflated poorly. The pulmonary artery was large and tense. A clot was present in the left atrium. The mitral valve was found to be tightly stenosed, with several calcified areas. During finger-fracture of the valve, the blood pressure became unobtainable and ventricular fibrillation occurred. Resuscitative measures were of no avail.

At autopsy, pertinent findings were confined to the heart and lungs. The heart weighed 550 gm., and the right atrium and ventricle were found to

be dilated. The left atrium contained two separate and organized thrombi, and a large calcified endocardial plaque was noted posteriorly. The mitral valve was markedly stenotic, admitting the forefinger with difficulty. The anteromedial cusp was calcified, and the posterolateral cusp was thickened and fibrotic. A recent commissurotomy 1 cm. in length was noted laterally. The aortic valve cusps were thickened, and the two posterior cusps were partly calcified. Moderate stenosis was present. The right ventricle measured 5 mm. in thickness; the left ventricle measured 12 mm. Although viewed grossly the coronary arteries appeared widely patent, microscopic sections revealed the right coronary artery to be narrowed 80% at several points. At one point an old hyalinized and recanalized thrombus was found.

The lungs appeared fibrotic, with several dense adhesions, and a pleural scar 2 cm. in diameter was noted in the superior segment of the right lower lobe. Several emphysematous blebs 1 to 2 cm. in diameter were present. Marked calcification of both pulmonary arteries had occurred, and a firmly adherent nonocclusive thrombus was found in the right main pulmonary artery. No free fluid, consolidation, or infarction was noted.

Anatomic diagnoses were rheumatic endocarditis with marked calcific mitral stenosis and moderate calcific aortic stenosis. There were old mural thrombi in the left atrium. Associated disease processes were coronary arteriosclerosis and pulmonary emphysema.

Comment.—Severe pulmonary vascular changes probably presented the primary difficulty in this patient. Where mitral stenosis is long-standing, it is often difficult to determine with certainty if the pulmonary or the mitral changes constitute the hemodynamically important block and whether the pulmonary changes are at least in part reversible or will continue to handicap the circulation despite the correction of the mitral stenosis. Associated coronary disease was still another factor contributing to the fatal outcome in this case.

CASE 7.—A 26-year-old white woman was admitted to the Good Samaritan Hospital in August, 1954, for cardiac catheterization in order to rule out the possibility of an interatrial septal defect which might complicate surgical correction of the stenotic mitral valve.

She had first had rheumatic fever at the age of 8 and had had frequent recurrent attacks. Also, she had suffered repeated bouts of hemoptysis. Dyspnea and fatigue were progressive. The patient had encountered considerable difficulty in the course of five pregnancies. She had a positive family history of rheumatic fever.

Relevant physical findings were confined to the cardiovascular system. The patient was normotensive, with a blood pressure of 118/76. Her pulse was regular; rate, 90. Her neck veins were distended, with visible systolic pulsations. Heart enlargement was Grade IV, with a parasternal lift. No thrill was palpable, and the point of maximal impulse was in the fifth intercostal space at the anterior axillary line. Heart tones were heard at all valve areas. P_2 was accentuated and split. Triple rhythm heard on various occasions by various observers was interpreted as an auricular sound. At the apex a rumbling mid- and late-diastolic murmur was heard, and a loud, blowing systolic murmur audible at the fourth intercostal space at the left sternal border was widely transmitted over most of the precordium but not to the axilla or back. The tender nonpulsating liver could be felt 2 fingerbreadths below the right costal margin.

Orthocardiograms revealed a mitral configuration of the cardiac silhouette, with enlargement of both atria. The hilar vessels were markedly exaggerated, with an increase in the peripheral lung markings. An electrocardiogram disclosed normal sinus rhythm, and there were tall P waves in Lead II, right axis deviation, and tall notched R waves in the right precordial leads—indicative of right ventricular hypertrophy.

The patient was in Class III-D in functional capacity; the diagnosis was mitral stenosis with associated tricuspid insufficiency. Cardiac catheterization was done because of the possibility of coexisting atrial septal defect: Pressure curves in the right atrium were in keeping with tricuspid insufficiency. No shunt was demonstrated, and pulmonary artery pressure was 75/30 mm. Hg. During the period of preoperative management, the patient's tricuspid insufficiency murmur disappeared completely.

Surgery was performed through a left thoracotomy incision. The pulmonary artery was found to be large and tense. No clots were in the atrium. Knife and finger were used to open the posterior commissure to the annulus, relieving the tight mitral stenosis. No thrills were found over the aorta.

In the postoperative period the patient received quinidine (0.2 gm. at six-hour intervals) to maintain normal sinus rhythm. On the third day the patient suddenly lost consciousness and, within a few minutes, was dead.

At autopsy the heart was found to weigh 600 gm. The pericardial cavity and the left atrium showed evidence of recent surgery. The surface of the left ventricle was noted to be covered by a fibrinosanguinous material. The right ventricle measured 5 mm. in thickness; the left ventricle, 13 mm. The tricuspid valve was found to be thickened, and it

measured 13.8 cm. in circumference. Several calcific plaques were noted in the pulmonary conus, and the mitral valve was thickened diffusely and extensively calcified. The chordae tendineae appeared short and thickened. The mitral valve revealed evidence of recent surgery, and it readily admitted a dilator 2 cm. in diameter. The aortic valve appeared essentially normal. Coronary vessels were patent, with no evidence of either old or recent occlusion. No congenital anomalies were observed. The foramen ovale was closed.

The right lung weighed 700 gm.; the left, 650 gm. No evidence of recent embolization or consolidation was seen. Grossly, portions of the pulmonary parenchyma appeared congested. Microscopically, the lungs showed patchy areas of hemosiderosis and chronic passive pulmonary congestion. The vessels demonstrated diffuse pulmonary arterial sclerosis.

The remainder of the autopsy examination disclosed only chronic passive congestion of the abdominal organs. No infarct or embolus was noted, in the brain or elsewhere. Anatomic diagnosis was rheumatic heart disease with inactive mitral valvulitis and mitral stenosis; chronic pulmonary arterial hypertension; chronic passive congestion of the liver and spleen.

Comment.—Although this patient was the youngest of our series, marked dilation of the pulmonary artery was present, with early arteriosclerotic changes in the smaller pulmonary vessels. In this patient we have an example of persons who encounter greatest difficulty during pregnancy or at any time when similar stress increases the burden of an already overworked left atrium, with resultant bouts of left atrial failure, pulmonary edema, and frank hemoptysis.

Tricuspid insufficiency, present early in this patient's hospital stay, cleared with adequate therapy. We are of the opinion that many apical systolic murmurs represent some degree of tricuspid insufficiency, even in the absence of classic findings such as systolic expansion of the cervical veins and a pulsating liver. Using cardiac catheterization, Sepulveda [46] recently has demonstrated tricuspid insufficiency in 60 of the 146 patients with predominant mitral stenosis; he was able to establish the diagnosis clinically in approximately 23% of the patients studied.

Ventricular fibrillation probably was the immediate cause of death. Although any relationship between the administration of quinidine and the sudden death of our patient is difficult to imagine, we have since abandoned the use of quinidine as a prophylactic measure in patients undergoing mitral commissurotomy.

MORTALITY

There were six deaths in this series. According to functional classification, mortality was as follows:

Class II	0 deaths in 7 patients (0%)
Class III	3 deaths in 50 patients (6%)
Class IV	3 deaths in 10 patients (30%)

Three of the six deaths were due to technical difficulties during surgery: In one instance the atrial wall was torn, with resultant fatal hemorrhage. A massive organized atrial thrombus made surgery impossible in another patient; immediately afterward, the thrombus occluded the valve completely, causing the patient's death. The surgical findings were confirmed at autopsy. In the third patient, advanced pulmonary emphysema and pulmonary fibrosis prevented complete collapse of the lung at the time of thoracotomy. Ventricular fibrillation occurred, and the patient died before definitive cardiac surgery was performed.

Our over-all mortality rate compares favorably with reports by Ellis and Harken: Among 500 patients under study, they reported a 6% mortality in Class III patients and a 25% mortality in patients in Class IV. Jones reported a 7% mortality in a series of 200 patients.

FOLLOW-UP OF OPERATIVE RESULTS

A follow-up was available in all patients who survived the operation. Approximately 75% of the patients were examined by the authors; the remainder were checked by their own physicians. Radiologic and electrocardiographic studies were available in addition to clinical evaluation for most patients. The minimum follow-up period was 1 year, and the maximum, 26 months, with an average period of 18 months. Both subjective improvement and objective findings were noted. A sizeable percentage of our patients reported excellent subjective improvement

TABLE 2.—*Follow-Up Results in Sixty-One Patients*

	Excellent		Good		Moderate		Unchanged		Worse		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Class II	3	43	2	29	1	14	1	14	..	..	7
Class III	29	62	13	28	3	6	1	2	1	2	47
Class IV	3	43	1	14	1	14	2	29	..	..	7
Total patients	..	57.5	..	26.5	..	8.0	..	6.5	..	1.5	..

which was not reflected in objective clinical findings. Results are summarized in Table 2.

None of the patients has died in the follow-up period. One patient who suffered right hemiplegia during surgery has made an excellent response from the cardiac standpoint but is still partially disabled with respect to motor function. As mentioned previously, none of the patients developed recognizable embolic episodes after discharge from the hospital. Only one patient's condition has deteriorated: she suffered reactivation of rheumatic fever, and has done rather poorly despite therapeutic measures.

SUMMARY

In this detailed study of patients who have undergone mitral surgery, emphasis is placed on the clinical appraisal of patients with especial attention to history, physical examination, and simple diagnostic tools readily available to most internists. Evidence is presented in support of the contention that relatively "pure" mitral stenosis can be diagnosed after careful clinical study with a high degree of accuracy.

Significant clinical improvement was obtained in 84% of the group. In addition, patients undergoing successful mitral surgery were afforded definite protection against embolic episodes. Over-all operative mortality was 9%; in good-risk patients, however, the mortality was appreciably lower.

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Case Reports

HODGKIN'S DISEASE OF THE RECTUM

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IN THE beginning of the 20th century it was generally believed that in Hodgkin's disease any part of the lymphatic system except the lymphatic tissue of the genitourinary, respiratory, and gastrointestinal tracts could be involved. However, Hess [1] already in 1907 had described a case of Hodgkin's granuloma localized in the sigmoid flexure and rectum with multiple small submucous nodules, some of which were slightly eroded. The same patient had an enlargement of the mediastinal lymph nodes, general lymphadenopathy, amyloidosis of the liver, and a large spleen. Histologically the lymph nodes and spleen revealed the presence of Paltauf-Sternberg cells, but unfortunately there is no mention of a microscopic examination of the lesions in the sigmoid or rectum. In 1913 Schlagenhaufer reported the first microscopically proved case of gastrointestinal localization of Hodgkin's disease.[2]

In recent years gastrointestinal lesions caused by Hodgkin's disease have been reported with increasing frequency. Hodgkin's disease of the gastrointestinal tract is most commonly localized in the lower part of the ileum in the area of Peyer's patches, just proximal to the ileocecal valve.[3] Localization of Hodgkin's disease in the rectum with or without generalized involvement of other organs has rarely been reported.

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REPORT OF CASE

We recently had the opportunity to study a patient who developed extensive involvement of the rectum associated with generalized Hodgkin's disease.

A 40-year-old white woman was admitted to the Beth-El Hospital on Feb. 2, 1954, with the chief complaint of abdominal cramps and signs of subacute intestinal obstruction. In July, 1949, a biopsy of an enlarged cervical lymph node had revealed the presence of Hodgkin's disease. A chest x-ray at the time also showed a large mediastinal mass about 9 cm. in diameter, which disappeared rapidly after x-ray treatment.

Subsequent to this the disease relapsed intermittently, with frequent localizations in cervical, mediastinal, and abdominal lymph nodes, for which the patient received many courses of x-ray radiation. In March, 1951, large paravertebral masses in the upper abdomen were present, which proved to be radioresistant. Nitrogen mustard was administered, resulting in considerable improvement. Thereafter nitrogen mustard treatment was repeatedly administered for recurrence of fever or lymph node swelling. In August, 1953, extensive herpes zoster developed over the lower abdomen, perineum, and right leg. In February, 1954, severe obstipation and abdominal cramps developed, at which time she was hospitalized at Beth-El Hospital.

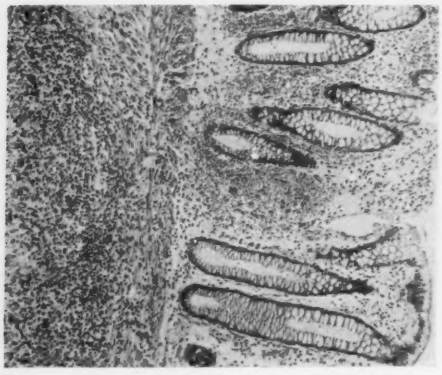
On physical examination both liver and spleen could be palpated but no lymph node enlargement was found. There was marked distention of the lower abdomen, and occasionally weak peristaltic waves were observed. On rectal examination a large tumor, displacing the rectum forward, could be palpated. Proctoscopy revealed bean-sized nodules infiltrating the rectal wall, resulting in a marked narrowing of the rectal ampulla. Several nodules had ulcerated surfaces, though the mucosa of the greater part of the lesions was intact. A ¾ in. proctoscope was introduced but could not pass the constriction 4 in. above the anus. A barium enema revealed extensive infiltration as well as forward displacement of the rectosigmoid (Fig. 1).

Fig. 1.—Before treatment. Note the filling defect in the proximal portion of the rectum. Of equal significance, note the marked retrorectal mass, as evidenced by the anterior displacement of the proximal rectum.

The patient received another course of nitrogen mustard therapy.

On Feb. 11, five days after nitrogen mustard therapy, all symptoms and signs of intestinal obstruction had disappeared and normal defecation returned. The abdomen was no longer distended. Digital examination revealed softening of the infiltrating nodules, and the retrorectal mass had shrunken to the size of a plum. At proctoscopy the surface of these nodules was seen to be intact, except for patches of hyperemia. The rectal lumen was less constricted, so that the same scope could now readily be advanced to 5 in. At this point

Fig. 2.—Photomicrograph showing rectum with infiltration of submucous layers by Hodgkin's disease; hematoxylin and eosin.



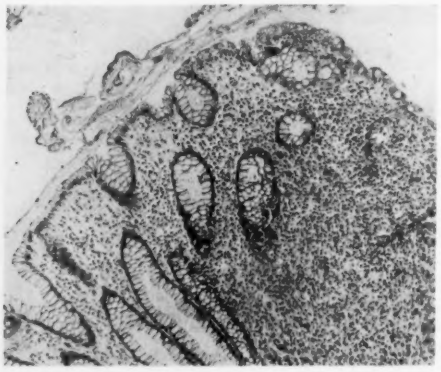


Fig. 3.—Photomicrograph showing rectum with infiltration of submucous layers by Hodgkin's disease; hematoxylin and eosin.

Fig. 4.—Three months after nitrogen mustard treatment. Filling defect again seen in the proximal rectum, as evidenced by irregularities in the contours and lack of distensibility. There is considerably less anterior displacement of the rectum, indicating the diminution in the size of the retrorectal mass.

the rectal mucosa was displaced posteriorly by whitish granulation tissue. This mass was biopsied, and the diagnosis of Hodgkin's disease of the rectum was confirmed histologically (Figs. 2 and 3).

The patient was febrile on admission, but the temperature came down to normal after administration of the nitrogen mustard. Just as had been the experience on previous occasions, she developed a marked allergic rhinitis after the nitrogen mustard injections, which improved after corticotropin-gel was administered. She was readmitted on May 6, 1954, for a further check-up. By digital rectal examination and by barium enema (Fig. 4) the retrorectal infiltration could still be demonstrated. The patient was seen again July 11, 1954, still in good health and comfortable, despite a potato-sized mass of nodules in and behind the rectum and an enlarged lymph gland in the right axilla. Her bowel movements were normal. She received x-ray treatment to the right axilla. In September, 1954, signs of polyneuritis developed. She had a numb sensation over both legs and both hands. Her gait was ataxic, and the tendon reflexes of both arms and legs were absent. In February, 1955, there were no gastrointestinal complaints and the findings on rectal examination had remained the same since July, 1954. Nitrogen mustard was given again because the spleen had not decreased in size. During the latest admission in April, 1955, the patient complained of pain radiating from the lower dorsal spine and engulfing the lower chest and upper abdomen. X-ray of the spine revealed sclerotic changes of the 10th and 11th dorsal vertebrae, suggesting the presence of Hodgkin's involvement. The polyneuritis was still present in June, 1955, although the pains in the legs were much less severe. The ataxia had diminished in intensity but had not disappeared. A barium enema in June, 1955 (Fig. 5), showed further shrinkage of the retrorectal lesion, with only scarring of the involved rectosigmoid. Throughout the numerous admissions a moderate anemia was always found. The white blood cells ranged from 5000 to 14,000. The number of eosinophilic cells never exceeded 3%. The sedimentation rate was always elevated, but it decreased temporarily after a course of nitrogen mustard therapy.

Fig. 5.—After one year and four months, during which time four nitrogen mustard treatments were administered. Irregular contours and lack of distensibility are again noted. Note, however, that the diseased portion of the rectum is lying in an almost normal position with reference to the sacrum, indicating almost complete disappearance of the retrorectal mass.

COMMENT

The accompanying Table summarizes cases of Hodgkin's disease of the rectum found in the literature.

In addition to the cases reported in detail, some observations of Hodgkin's disease of the rectum are casually mentioned in discussions or statistical reviews. Siegmund [13] reported one case of a 68-year-old man with a 5 cm. long tumor of the rectum which histopathologically was diagnosed as Hodg-

	Age, Yr.	Sex	(a) Duration of Symptoms (b) Clinical Manifestations (c) Morphological Blood Picture (d) Clinical Diagnosis	Part of Gastrointestinal Tract Involved	Lymph Nodes & Other Organs Involved	Types of Gross Change in the Gastrointestinal Tract & Associated Pathologic Changes
1. Hess (1907) [1]	24	M	(a) about 1 yr. (b) diarrhea & abdominal distention (c) ..... (d) cirrhosis of the liver, secondary anemia	Colon & rectum	Cervical, inguinal, mediastinal, mesenteric; spleen	Diffuse infiltration of the involved segments of the gastrointestinal tract
2. Schlagenhaufer (2d case) (1920) [4]	47	M	(a) a few weeks (b) abdominal pain, constipation followed by diarrhea, anorexia, melena, distention of abdomen, intermittent fever (c) ..... (d) gastric & intestinal ulcers (tuberculous?)	Stomach, small & large bowel, rectum	None	Diffuse infiltration of stomach; localized infiltration of bowel; many superficial ulcers
3. Terplan (1922) [5]	56	F	(a) several weeks (b) constipation followed by diarrhea, firm mass palpable below left costal margin, abdominal distention & pain increasing on palpation, fever intermittent for one week, then normal temperature (c) ..... (d) intestinal tumors, tuberculous enteritis (?)	Stomach, small bowel & rectum	Cervical, perigastric, mesenteric, peripancreatic, periaortic, perirectal; spleen, liver	Many small ulcers & infiltrations in the stomach; many ulcers in large & small bowel; in the rectum many ulcers were confluent; their base was grayish-green; their edges were red; the rest of the mucosa was dark red; there were also tiny up to pea-size gray infiltrations, some of which had an eroded surface; ulcer of the tongue, acute peritonitis
4. Sussig (1st case) (1924) [6]	52	F	(a) 7 mo. (b) loss of weight, diarrhea with occasional mucus and blood; proctoscopic examination: swollen & reddened mucosa, prominent follicles, many scattered tiny superficial ulcers with slightly elevated edges & surface covered with a thin layer of blood (c) RBC 3,652,000; WBC 3,200; P 80%, L 15%, Eo 5%* (d) ulcerative rectosigmoiditis	Stomach, ileum, colon, rectum	Cervical, mesenteric, retroperitoneal; spleen, liver	Ulcer 2 cm. in diameter & multiple small ulcers in the stomach; multiple pea-sized ulcers in ileum, colon, and rectum
5. Sussig (2d case) (1924) [6]	42	M	(a) 6 wk. (b) epigastric pain, anorexia, nausea, stool with mucus and blood, rapid loss of weight, distention of abdomen, high fever, type not stated (c) RBC 2,420,000; WBC 4,800; L 18%; Eo 1% (d) Carcinoma of large bowel or tuberculous lymphoma of mesentery	Jejunum, colon, rectum	Axillary, inguinal, mesenteric, retroperitoneal	Multiple small ulcers in jejunum, large bowel, & rectum; perforation of jejunum ulcer; ascites
6. Hayden & Apfelbach (3d case) (1927) [7]	44	F	(a) 18 mo. (b) onset with swelling of right side of face, then enlargement of a single cervical node, followed 6 mo. later by abdominal pain, distention, and constipation; frozen pelvis & infiltration of rectal wall; temperature intermittent, seldom exceeding 100 F (c) WBC 8,300; 2 mo. later WBC 5,800, Hb. 80%; 6 mo. later WBC 7,000, Hb. 50% (d) neoplasm of sarcoma type	Stomach, duodenum, rectum	Right cervical, perigastric, periaortic, gastrohepatic, omental, iliac; spleen, ovaries	Multiple small ulcers 1 to 10 mm. in diameter and 1 to 2 mm. deep; one 5 cm. long ulcer & infiltration of the submucosa of the wall of the stomach; in rectum 2 cm. above anal margin there was a smooth single oval mass 13×8 mm. & 4 mm. high with 1 mm. center umbilicated & ulcerated; in addition, there were multiple oval or round elevations; ascites
7. Martin (1936) [8]	55	M	(a) 4 yr. (b) enlarged inguinal nodes, grinding epigastric pain relieved by food & soda, stool positive for occult blood, x-ray involvement of stomach & duodenum, temperature normal (c) RBC 4,950,000; WBC 7,500 (d) Hodgkin's disease	Stomach, duodenum, small intestine, rectum	Generalized adenopathy; spleen	Mention is made only of a large mass involving the rectum

Hodgkin's Disease of Rectum—Continued

		Age, Yr.	Sex	(a) Duration of Symptoms (b) Clinical Manifestations (c) Morphological Blood Picture (d) Clinical Diagnosis	Part of Gastro-intestinal Tract Involved	Lymph Nodes & Other Organs Involved	Types of Gross Change in the Gastrointestinal Tract & Associated Pathologic Changes
8.	Gallart, Mones, & Roca de Villart (1938) [9]	35	F	(a) 2 yr. (b) constipation, tenesmus, distention, occasionally bloody stools, loss of weight, anorexia; 2 cm. above the anus, a hard mass the size of a nut, surrounded by many smaller nodules, was felt; the mass bled easily on palpation; proctoscopy showed a very vascular mass on the right lateral side of the lower part of the rectum; temperature elevated nightly, 37.6 to 39.6 C (c) RBC 2,000,000; Hb. 40%; WBC, 4,900; P 63%; L 30%; M 7%;* toxic granulation of polymorphonuclear cells (d) Hodgkin's disease	Rectum	Inguinal; spleen, liver	Infiltration of the mucosa, submucosa, & muscularis
9.	Spiesman & Rubenstein (1942) [10]	24	F	(a) 8 yr. (b) condition started with cough, fever (100.8 F), and enlarged nodes in right supraclavicular region, both axillae, & right hilus; deep x-ray therapy of different manifestations was repeatedly successful; during the 8th year of the disease frequent mucosanguinous stools and marked tenesmus developed, alternating with obstipation; a firm infiltrated constricting ring in the rectal ampulla about 4 in. above the anal opening was found, which barely permitted the passage of the examining finger; x-ray therapy resulted in little improvement of the rectal symptoms; progressive wasting led to death (c) RBC 4,000,000 in the beginning of the disease; WBC 24,900; P 80%; L 16%; B 2%; Eo 2%* (d) Hodgkin's disease	Sigmoid, rectum	Supraclavicular, axillae, mediastinal, retroperitoneal	Constriction rings in the rectum and sigmoid; edema of left arm, both lower extremities, & nonfunctioning kidney
10.	Craver & Herrmann (1946) [11]	22	F	(a) 12 yr. (b) lower abdominal pain, diarrhea, vomiting; a firm lobulated mass was present outside the rectal wall & posterior to it; other masses were palpable throughout the lower abdomen (c) ..... (d) Hodgkin's disease	Rectum	Cervical, axillae	Proctoscopic examination revealed stenosis about 8 cm. up and grayish-white thickened fold in this location
11.	Pettinari (1947) [12]	40	M	(a) ..... (b) heaviness in the rectum, purosanguinous discharge, no constipation, typical intermittent fever of Pel-Ebstein type (c) normal; later leucocytosis with eosinophilia (d) Hodgkin's disease	Rectum	No signs of dissemination; no autopsy	Small apple-sized tumor about 5 cm. from anus surrounded by small nodules

* P, polymorphonuclear cells; L, lymphocytes; Eo, eosinophiles; M, monocytes; B, basophiles.

kin's disease. Pettinari [12] mentions that Bini and Parvis reported a case of diffuse gastrointestinal Hodgkin's disease with involvement of the rectum in a 25-year-old man. In a discussion of genitourinary tract lesions in Hodgkin's disease, Melicow [14] mentions a case of Hodgkin's disease behind the rectum in the hollow of the sacrum. No details are given.

Incidence.—A careful study of all reported cases of Hodgkin's disease of the rectum emphasizes the rarity of this localization, although statistics of different investigators vary greatly. Lame and others [15] found 20% of the malignant tumors of the stomach and 50% of the malignancies of the small intestine to be lymphomas—an unusually high incidence. However, none of their 22 reported cases of lymphoma was localized in the rectum. Symmers [16] reported that in a series of 173 necropsies of patients with Hodgkin's disease not one example of involvement of the gastrointestinal tract was found. Migliaccio and Pahigian [17] reviewed the material of gastrointestinal neoplasms over a period of 20 years. They found 1490 cases of adenocarcinoma and 36 cases of Hodgkin's disease, but there was involvement of the rectum in none of the latter. In a study of 174 cases of Hodgkin's disease, Jackson and Parker [18] found 9 cases of gastrointestinal involvement; none of these 9 cases was localized in the rectum. The statistics of Warren and Lulenski [19] differ from those reported by the other investigators. They reported 13 cases of gastrointestinal Hodgkin's disease, 8 of which were localized in the colon and 3, in the rectum. Somewhat high also is the incidence of involvement of the rectum in Martin's [8] series of lymphomas. Of his 19 cases, 1 was localized in the cecum, with infiltration of the bladder and the rectum. In one case, localized in the stomach, proctoscopic examination showed cartilaginous thickening of the rectal valves associated with numerous ulcers which did not resemble carcinoma. This report, however, is based on Mallory's classification, which does not distinguish between Hodgkin's disease, lymphogranuloma, lymphosarcoma, leukemia, or aleukemia, but uses the designation lymphoma indiscriminately for all these diseases.

Pathogenesis. — Coronini [20] discusses the differences of opinion about the problem of the histogenesis of gastrointestinal Hodgkin's disease. Eberstadt [21] defends the theory that this localization results from primary nodular infiltration of the lymphoid tissue of the submucosa, which then protrudes into the lumen or invades the other layers of the bowel. Hauck [22] and Ceelen and Rabinowitsch [23] are of the opinion that the process may reach the intestinal tract by direct extension from the involved mesentery or by retrograde lymphatic transport from the mesenteric nodes. Siegmund's findings of isolated granulomatous lesions in the submucosa support Eberstadt's hypothesis. There may well be cases of rectal Hodgkin's disease in which lesions arise in the wall of the rectum. In our case, however, as in many other cases, the impression is obtained that the process started in the retroperitoneal nodes and extended into the wall of the rectum.

Gross Pathology.—The gross pathology of Hodgkin's disease of the rectum as described by Terplan,[5] Symmers,[16] and others * may assume several forms. It may consist of a flat circular infiltration leading to a rectal stenosis or of small or large nodules with or without ulceration. The ulcers, varying in size and depth, have an irregular elevated edge and usually are of white-grayish color and hard in consistency. They often are deeply penetrating in character and may even invade the muscularis.

Age and Sex.—Just as is the case in the commoner localizations of this disease, Hodgkin's disease of the rectum occurs in the third, fourth, and fifth decades of life. The frequency is the same in men as in women.

Clinical Picture.—The clinical picture of Hodgkin's disease of the rectum is mainly

* References 24 and 25.

characterized by signs of obstruction or infiltration, i. e., pain; change in bowel function, leading to obstipation or even ileus; bleeding, and the presence of a palpable mass. Often the general symptoms and signs of Hodgkin's disease can be found, i. e., Pel-Ebstein's recurrent fever, pruritus of the skin, loss of weight, anemia, leucocytosis, polynucleosis, and eosinophilia. Some authors found anemia to be rare in gastrointestinal Hodgkin's disease.

Differential Diagnosis.[10]—Other benign tumors of the rectum, such as fibroma, lipoma, adenoma, angioma, adenomyoma, and fibromyoma, and malignant tumors like sarcoma, melanoma, and carcinoma can produce rectal stenosis. All these diseases, except carcinoma, are rarities, and a biopsy will reveal the correct diagnosis. The anorectal stricture of lymphogranuloma venereum is usually found in 25- to 45-year-old Negro women. The palpating finger easily recognizes the funnel-like obstruction of the rectum, usually localized a few centimeters above the anus. Only occasionally, irregular multiple constrictions and lateral pockets filled with soft granulation tissue are encountered. These patients are obstipated and allegedly eliminate a "cherry-juice-like discharge." A positive Frei test and a biopsy showing granulation tissue reveal the diagnosis. Tuberculous stricture of the rectum is rare and should only be considered in the presence of active tuberculosis of the lung. In the scrapings from tuberculosis of the rectum Mycobacterium tuberculosis can usually be found. Syphilitic rectal strictures of the ulcerative-fibrotic type have become very rare indeed. The history, the positive serologic reaction, and the favorable response of the ulcerations to specific therapy are sufficient for the diagnosis. In amebic granuloma rapidly moving amebic trophozoites are found in a direct smear from the rectal lesions and the cultures for Amoeba histolytica are positive. Ulcerative proctitis may clinically resemble Hodgkin's disease of the rectum. Usually general debility, cachexia, diarrhea, and irregular fever are present. Stenosis develops in a much later stage than in Hodgkin's disease. The Frei test and Wassermann reaction are negative, and the biopsy shows granulation tissue but no typical Hodgkin's disease. Postradiation proctitis and stricture frequently follow x-ray or radium therapy of a malignant tumor of the pelvic organs. The mucosa around the lesions shows extensive formation of telangiectasis; the biopsy shows only nonspecific granulation tissue. Strictures of external origin, such as are seen in carcinoma of the prostate, chordoma, sarcoma, dermoid cyst, Krukenberg tumor, tumors of pelvic organs pressing on the rectum, and pelvic abscess, usually do not cause ulcerations of the mucosa as commonly occur in Hodgkin's disease. If, as rarely happens in carcinoma of the prostate, the extrinsic tumor perforates through the rectal mucosa, a biopsy solves the problem.

In general it can be said that palpation and proctoscopy are important for the diagnosis of Hodgkin's disease of the rectum but that only a positive biopsy can eliminate all diagnostic doubts.

Prognosis.—Minot and Isaacs,[26] in their analysis of a large group of lymphomas, concluded that the duration of life was longer in the patients with symptoms referable to the gastrointestinal tract. In contrast, Craver and Herrmann [11] found that life expectancy was short, 9 to 12 months, when the initial lesions of Hodgkin's disease are localized in the gastrointestinal tract.

The observation by Minot and Isaacs can perhaps be explained by the experience that the gastrointestinal complications of Hodgkin's disease usually develop in the later stages of the disease, i. e., in patients who have suffered from the disease for several years. It has been brought out † that even if the retroperitoneal and retrorectal lymph nodes are involved early in the disease symptoms and signs will only develop in the later stages. For a long time the abdominal organs are able to adjust to the space-

† References 27-29.

occupying masses. Only when the viscera can no longer accommodate themselves to the enlargement of the masses will pressure symptoms arise. Hence the obstructive syndrome is a late manifestation and arises only in these patients who live long enough to develop it. It seems that our patient's course serves to bear out this concept.

Therapy.—Nitrogen mustard and radiation therapy do not change the ultimate outlook of the disease, but they will often relieve the patients for more or less prolonged periods. When these methods are applied for the first time, results may seem little short of miraculous. At subsequent series of treatment the disease becomes more and more resistant. Investigators ‡ who have vast experience in the treatment of Hodgkin's disease consider x-ray therapy most effective in the localized form of this disease and nitrogen mustard the therapy of choice in instances of generalized adenopathy.

SUMMARY

A case of extensive lymphogranulomatous rectal lesion in a patient with generalized Hodgkin's disease is presented. A review of the literature of Hodgkin's disease of the rectum is given. The incidence, clinical features, gross and micropathological findings, differential diagnosis, prognosis, and treatment are discussed.

Dr. I. Snapper, Director of Medicine and Medical Education, Beth-El Hospital, gave guidance and help in the preparation of this paper.

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IDIOPATHIC HYPERLIPEMIA ASSOCIATED WITH CORONARY ATHEROSCLEROSIS

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THE CLINICAL syndrome of idiopathic hyperlipemia has been described fully in several recent surveys.* In essence it embodies a triad of signs and symptoms which include abdominal pain, hepatosplenomegaly, and cutaneous xanthomata with an elevated fasting level of serum neutral fat. Increase of serum neutral fat may also be seen in diabetes mellitus, nephrosis, alcoholic cirrhosis, hypothyroidism, and glycogen-storage disease. In the absence of other causative disease, hyperlipemia may be termed idiopathic.[5] Although it has been suspected that this disorder of lipid metabolism might predispose to coronary atherosclerosis, as yet no pathological reports of such association have been found. That hyperlipemia may be associated with coronary artery disease has been demonstrated clinically.† The single report in the literature of the postmortem findings in a case of idiopathic hyperlipemia revealed no evidence of coronary atherosclerosis, with death being due to an intercurrent infection.[7] The following case history records the postmortem findings in a patient with idiopathic hyperlipemia associated with coronary atherosclerosis.

REPORT OF CASE

A 39-year-old white male undertaker was admitted to the hospital on Dec. 2, 1954, complaining of shortness of breath upon exertion and recurrent epigastric and substernal "pressing" pain. His illness began nine months before admission with sudden onset of severe substernal and precordial chest pain radiating to both shoulders and arms. An electrocardiogram revealed an anterior myocardial infarction. He was placed on bed rest for 10 weeks but since that time had been unable to walk one block without symptoms of dyspnea and substernal pain, interpreted by the patient as "gas," which was partially relieved by eructation. Similar episodes occasionally followed eating. The past history was relevant in that for 10 years he had noted intolerance to greasy foods, manifested by a feeling of fullness and pain in the epigastrium. The patient's mother died at age 68 of a "heart attack," and one brother died of leukemia.

Physical examination revealed a well-developed and well-nourished man weighing 165 lb. and measuring 72 in. in height. The blood pressure was 110/70. The skin over the forehead was a mottled light tan. The heart was not enlarged to percussion, and the rhythm was regular. There were no cardiac murmurs, and the sounds were of fair quality. The lungs were clear to auscultation. The tip of the spleen was questionably felt. The results of physical examination were otherwise normal.

Laboratory examination revealed red and white blood cell counts, hemoglobin determination, differential leucocyte count, and sedimentation rate to be normal. Urinalysis was negative except for a "trace of glucose." Fasting blood sugar was 107 mg. on two occasions. Serological test for syphilis was negative. Serum protein was 7.2 gm/100 ml., with 5.2 gm. of albumin. Total serum lipids were 2132 mg/100 ml. (normal, 600-800 mg.), with cholesterol 450 mg/100 ml. Sulfobromophthalein (Bromsulfalein) test revealed 1% retention after 45 minutes. The prothrombin time was 98% of normal and the BMR was +9%.

Roentgen examination of the chest was interpreted as normal. Upper gastrointestinal series revealed prolapse of gastric mucosa, and oral cholecystography showed a well-visualized gall bladder. An electrocardiogram suggested an old anteroseptal myocardial infarction. A ballistocardiogram was of Grade III abnormality (Fig. 1). A vitamin-A-tolerance test revealed a fasting level of 78γ per 100 cc., with a marked rise within five hours to a level of 1080γ per 100 cc. (Fig. 2). Lactescence of serum was seen in all samples. Carotene level was constant at 259γ per 100 cc. A blood specimen from the

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* References 1-4.

† References 1, 2, and 6.

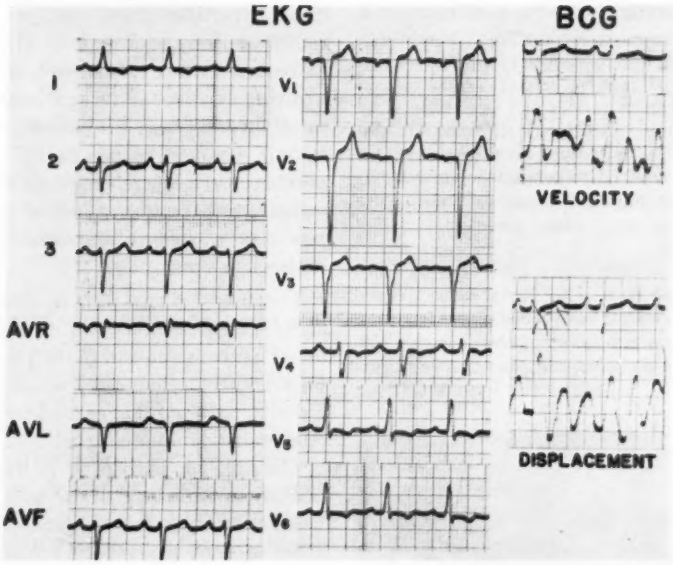
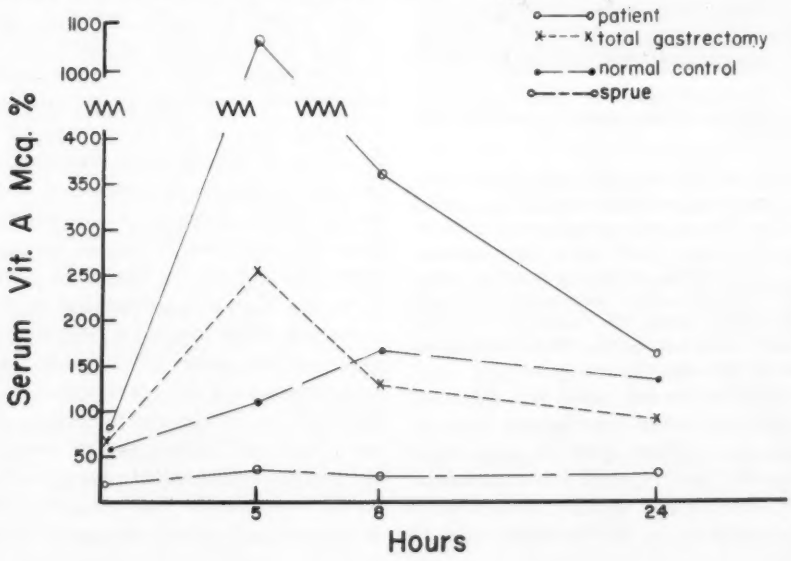


Fig. 1.—Electrocardiogram and ballistocardiogram done upon admission to the hospital. The former reveals an old anteroseptal myocardial infarction.

patient's father was obtained for serum lipid determination, and serum lipid was found to be 1238 mg/100 cc., with cholesterol 400 mg/100 cc.

Treatment consisted of a 20 gm. low-fat diet. One week later total serum lipids were 1120 mg/100 cc., with cholesterol 375 mg/100 cc., and cholesterol esters 59%, phospholipids 190 mg/100 cc., fatty acids 780 mg/100 cc., and neutral fat 478 mg/100 cc. (normal 0 to 150 mg.).[8] By the third week of treatment the patient's symptoms of epigastric and

Fig. 2.—Vitamin-A-tolerance test (3000γ vitamin A, U. S. P., per pound body weight). Note marked rise in patient's test in comparison with the normal and those of a patient with sprue and another with total absence of the stomach.



substernal pain had subsided and the total serum lipids had decreased to 618 mg/100 cc. and cholesterol, to 232 mg/100 cc. However, on two occasions after intentional high-fat feedings symptoms returned for transient periods and were relieved by glyceryl trinitrate (nitroglycerin). On the 37th hospital day, while sitting down, the patient developed a sudden episode of substernal pain and immediately took glyceryl trinitrate, 0.45 mg. sublingually. He fell to the floor unconscious, convulsed, and died five minutes later.

Autopsy done eight hours after death revealed moderate enlargement of the heart, which weighed 420 gm., and extreme constriction of the lumina of both coronary arteries due to atherosclerosis with evidence of old occlusion and recanalization of both vessels (Fig. 3). A small area of fresh hemorrhage

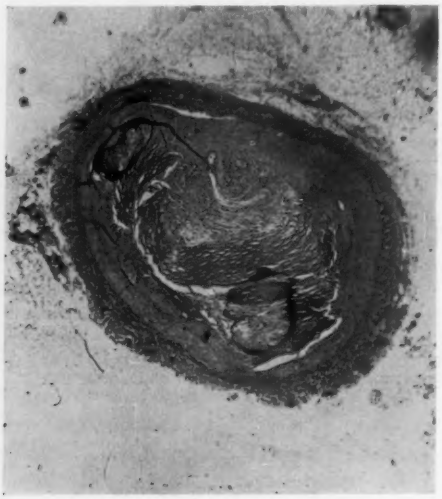


Fig. 3.—Photomicrograph of right coronary artery, revealing severe atherosclerosis, occlusion, and recanalization.

was seen in the wall of the proximal portion of the right coronary artery. A large thinned and scarred area of the left anterior ventricular wall and adjacent septum was found which microscopically showed severe diffuse ischemic myocardial degeneration. There was passive congestion of the lungs and abdominal viscera. The pancreas, liver, and spleen were otherwise normal. Moderately severe generalized arteriosclerosis was present.

In 1932 Bueger and Grutz first described idiopathic or essential hyperlipemia in an 11-year-old boy.[5] More than 50 cases have subsequently been reported in the literature. Recent evidence has appeared to indicate a familial tendency in this disorder. Lever[1] found hyperlipemia recorded in 1 or more family members of 7 patients in a review of 41 reported cases. Malmros[2] in a study of all living relatives of two patients with idiopathic hyperlipemia discovered the disorder in four members of one family and in one member of the other. Only one relative (the patient's father) was examined in the above case report, and an abnormal elevation of serum lipids was noted.

The disease occurs in both sexes and at all ages.[4] Xanthomatous skin lesions have been found in about one-half of the reported cases. Hepatosplenomegaly is occasionally seen and is due to fat deposition in the liver and spleen. Abdominal pain may occur. The mechanism is obscure, but perhaps it is due to lacteal distention, stretching of the liver capsule by hepatic enlargement, or pancreatitis.[9] Episodes of acute pancreatitis are seen in about 14% of cases.[10] Whether hyperlipemia predisposes to the pancreatitis, or vice versa, remains conjectural.[1]

The mechanism of production of elevated serum lipids in these patients has been termed a retention hyperlipemia and has been thought due to failure of liver and fat depots to remove dietary lipids from the blood stream at a normal rate.[5] Support of this idea is derived from the study of patients given I^{131}-tagged neutral fat orally, in whom there is found a prolonged rate of iodine clearance from the blood.[11] The use of the vitamin-A-tolerance test in our patient similarly reflects a striking delay in the clearance of fat from the serum, it being assumed that the absorption and blood stream clearing of this fat-soluble vitamin given in an oily vehicle corresponds proportionally to the behavior of orally ingested neutral fats.[12] In Figure 2 it is seen that this patient had a 10-fold increase in serum vitamin A over the normal control at five hours. This would support the hypothesis of a delayed clearance from the blood stream. It may also indicate an abnormally increased absorption of vitamin A. Gofman has indicated that patients with idiopathic hyperlipemia have elevations of the lipoprotein molecules of the classes $S_{f\ 100\text{-}400}$,

which are normally elevated after the ingestion of dietary fat,[13] i. e., during alimentary hyperlipemia.

The prognosis in this disorder has been thought benign, with no fatalities due to the disease reported to the present time. Joyner first suggested in 1953 that such persons would seem more likely to develop atherosclerosis than a person with normal fat metabolism.[4] The hyperlipemia and hypercholesteremia in these patients should leave little doubt as to the potentiality of this complication, since the association of these two factors with atherosclerosis is well documented.[14] Others have noted the presence of clinical coronary artery disease manifested by angina pectoris or myocardial infarction.‡ Pathological data in the present case clearly suggest this association. It is generally agreed that atherosclerosis represents a fault in the metabolism of fats in which blood lipids are probably deposited in the subintimal tissues of arteries. Present studies of the etiology of atherosclerosis have placed most of the emphasis upon an abnormal elevation of various serum lipid fractions, the levels of which are affected by patterns of heredity, by certain disease states, and by ingestion of dietary fats.[14] Keys has established the importance of dietary fats in the etiology of this disease in a study of persons with different dietary habits.[16] With the average American diet containing approximately 40% of total calories in the form of fats, it follows that patients with retention hyperlipemia (i. e., idiopathic hyperlipemia) are subject to very high levels of total serum lipids and consequently to a strong predisposition to the development of atherosclerosis. When ingestion of dietary fat is curtailed, such patients are usually able to avoid these high lipid levels and are benefited as a result.

The clinical response of this patient to a low-fat diet was striking, since within three weeks of dietary fat restriction symptoms of epigastric and substernal distress subsided and total serum lipids were lowered from 2132 mg. to 618 mg/100 cc. Malmros noted a striking relief of angina pectoris with fat restriction in the diet,[2] while others have produced angina pectoris with high-fat feedings.[17] Considerable reduction of serum lipid values has also been attained by prolonged administration of heparin, and this has been recommended in the treatment of patients with idiopathic hyperlipemia in whom a low-fat diet fails to bring about an adequate fall in serum lipids.§ This substance accelerates the physiologic process of conversion of higher S_f classes into lower ones, probably through activation of a serum clearing factor rather than through any direct action of the drug itself.

The screening of fasting blood specimens for serum turbidity presents a simple and reliable method for the detection of patients with hyperlipemia.‖ Determinations of serum lipoprotein and total lipid values and the use of vitamin-A-tolerance and other fat-tolerance tests offer additional diagnostic methods. In any patient with suspected coronary artery disease or other evidence of atherosclerosis it would seem reasonable to perform some of these tests to exclude the association of a treatable disease such as idiopathic hyperlipemia.

SUMMARY

A case is presented of idiopathic hyperlipemia with severe coronary atherosclerosis and coronary occlusion, with myocardial infarction demonstrated at autopsy. Although idiopathic hyperlipemia is recognized to be associated with clinical coronary artery disease, this is the first recorded case of idiopathic hyperlipemia with postmortem evidence of coronary atherosclerosis. The vitamin-A-tolerance test revealed a marked decrease in tolerance, with extremely high levels of serum vitamin A at five hours, supporting the prevailing concept of the pathologic physiology of this entity, i. e., an impaired or delayed clearance of dietary fats from the serum. The treatment of this disease consists of a low-fat diet, which often

‡ References 1, 2, 6, 15, and 17.

§ References 4, 6, and 15.

‖ References 2 and 17.

results in prompt alleviation of symptoms of angina pectoris and abdominal pain often seen in these patients. Heparin given intramuscularly or intravenously may be helpful if dietary control is not effective.

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Books

EDITED BY WILLIAM B. BEAN, M.D.

SOME MUSINGS ON REVIEWING MEDICAL BOOKS

> The images of men's wits and knowledges remain in *books*, exempted from the wrong of time and capable of perpetual renovation. Neither are they fitly to be called images, because they generate still, and cast their seeds in the minds of others, provoking and causing infinite actions and opinions in succeeding ages. So that if the invention of the ship was thought so noble, which carrieth riches and commodities from place to place, . . . how much more are letters to be magnified, which as ships pass through the vast seas of time, and make ages so distant to participate of the wisdom, illuminations, and inventions, the one of the other?
>
> LORD BACON, "The Advancement of Learning"

RECENTLY I accepted the chore of being Book Review Editor for the A. M. A. ARCHIVES OF INTERNAL MEDICINE. This was the result of no mere whim. It came after a long but intermittent contemplation of the state of book reviewing in contemporary medical journals. As far as I can find, books are reviewed in the majority of medical and scientific journals without any particular system, program, or purpose. My willingness to assume this burden was based on my belief in the potential benefits of critical reviewing of medical books and acute awareness of the deficiency of present-day medicine, and indeed of all science, in not having any internal forum for criticism, critique, and speculative discussion. Such themes occasionally occupy the windy rumblings of presidential addresses, and perhaps the secret sessions of the self-important. Still, there is no recognized place to which the just and honest can repair for words of counsel, of wisdom, and of carefully considered opinion. If the contemporary criticism continues to be *of* doctors but *by* and *for* laymen, we will continue to get the bias of the half-truth based on half-fact, or distortion born of illness. Today much of the world lives beset with paranoia, with fear, with a view of the rest of the world as evil. Somebody will steal this idea or that; the laboratory and records must be locked like a bank vault. There is danger from our neighbors, peril over the hill, and doom beyond the horizon. Such polarizations are not without effect. They determine our practices, and thus influence the direction of the future. If such practices are to be our policy we should understand the consequences. If they are hurtful, the first step in removal is to recognize them.

Today medicine's need for an internal critique is even greater than the need of general science for self-correcting forces. Medicine is a curious mixture of arts and science. Where its practice accomplishes useful ends the arts retain their primacy and provide the medium through which science is applied to the welfare of patients. An inner critique has provided self-correcting and adjusting forces in the graphic arts, drama, and music. Politics has its correctives, be they election or revolution. But medicine has never had an effective forum for critique within, and only at times fair criticism from outside. Since the conserving arts of medicine, though essential, tend to hold back progress if not examined and refreshed by the experiment and experience of practice, and since the essential characteristic of

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science is that it is provisional, forever being finished but never finished, *change* is the life blood of medicine. But change, unless directed, rarely correlates with progress. The crucial and painful defect of present-day medical practice is the lack of effective critical introspection. A deficiency of the catalytic enzyme, criticism, can be harmful, can produce as much morbidity and mortality in medical practice, teaching, and research as a vitamin deficiency can produce in a growing, living creature.

The following comments are merely a selection from many which might have been chosen. They represent opinion, not dogma. The aims of this section, though unlikely to be realized in full, provide incentive, challenge, and a working plan. Anyone who has ever set himself to write a critical review will recognize the difficulties and hazards of any such undertaking.

Anonymity.—It is believed by some critics and book reviewers that the reviewer is inhibited by having to attach his name to the review.* This is hardly a courageous philosophy. If one is unwilling to be known, to have his opinion counted as *his* opinion, it is unwise for him to sign his name to anything he writes. Carried to an extreme, this policy becomes the method of the anonymous letter. If we feel obliged to say unpleasant or unfavorable things of a child or neighbor it must be done face to face. Likewise in criticism of books what we say may appear to us to be urgent matters and critical too. It is only fair that a book's author and publisher know who the critic is. Of course, certain sensitive souls cannot bear criticism. No one of us is made happy by it. Calming down after the first hostile urges have cooled lets the judicious gain help from criticism. If we cannot face it we should not write a book in the first place. An uncriticizable book is a perfect book. However hard authors strive, they have not yet arrived at perfection. This is especially true when the author is a successful physician. Praise from patients may have given him the illusion of perfection and power, beneath which he hides. He hardly suspects his own intellectual innocence.

An opposite aspect of anonymity concerns writing for current medical journals. I have often wondered if "this monstrous regiment" of medical articles published in contemporary American journals would not be reduced to a dribble if the author's name were not published. This, however, is not a serious proposal to help dam up the torrent of "literature." One of the legitimate ambitions of investigators, physicians, and scientists is to be recognized by their peers for work well done and ably reported. And the same incentive applies to reviews and reviewers of medical books.

The book reviewer's life would be quieter and more unmolested if he could honestly praise all books he reviewed or review only books he could praise. To reduce the florid growth of useless and sometimes dangerous books, dangerous because of error and confusion, book reviewing in these columns will aim for whatever values and virtues exist in thoughtful criticism. Such criticism must be fair, not punitive. At the same time it must be recognized that it is no more than the opinion of one specific person. It will not be the homogenized structureless consensus of a committee reflecting the watered-down equivalent of a folk song, the blended anonymity of the unknown soldier, and that bleak and barren statistic, the common man or the man in the street.

* The "now you see it, now you don't" of names signed to reviews of this section in the last few months reveals erratic use of backlog rather than ambivalent policy. It is a risk whenever printer, publisher, editor, and assistants are in different places.

In our day of yearning for support and comfort, for facts, for final knowledge, we have accepted as infallible and eternal truth the pontifications of those draped in the external vestments of authority. There is no such thing as the composite mind of the editorial board or the composite mind of book reviewers or critics. Opinions cannot exist as detached and separate from the person who writes a review. The reviews to be printed here are not the offspring of a committee or caucus. Nor will they be, as many current medical texts are, the unconnected but assembled accretions of a miscellaneous multitude of separate contributors. Such contributions frequently have no essential connection or common focus. They are jumbled together as strange bedfellows within the covers of a book. Frank criticism is the aim, and review will be related to first view as research is related to search. While we shall strive to make reviews objective and critical, there is no claim of infallibility and no notion of exemption from error. The theme we will try to abide by is expressed in Jefferson's words about the University of Virginia: "For here we are not afraid to follow truth wherever it may lead, nor to tolerate any error so long as reason is left free to combat it."

The Selection of Books.—Much research is directed by the instinct of the applicant concerning the whim of the board, agency, or committee which grants money for research. Likewise the book reviews in many contemporary medical journals have no more direction than to accept blindly whatever flotsam and jetsam happen to be washed up on the shore. Not all books sent to journals are reviewed, but little effort is made to obtain valuable new books which do not arrive for review. An alert book review section should include critical selection of books for review as well as critical review of books selected. This difficulty may be resolved along several lines. Improving the quality of book reviews encourages publishers and authors of good books to have the books reviewed. At the same time, it diminishes the enthusiasm of authors or publishers whose medical books, while perhaps commanding a respectable market, present a melancholy spectacle of error, ineptitude, and inadequacy. The selection of books also presents the problem of a selection of reviewers. Medicine is not without its Mr. Milquetoasts. It takes much personal knowledge of people and of doctors to find those who are critical and are willing to be named at the same time. I am convinced that such people can be found and can be prevailed upon to provide valuable criticisms. The process will be slow.

The reward for writing a book review in medical journals is no more cogent lure than getting a present of the book which is reviewed. While this may help build up a library, it is small incentive to build up the quality of reviews. It is representative of the large amount of hack work done by physicians as editors and authors of books, articles, and reviews. The urge to write is strong. The urge to write well is weak, too weak for most of us to use the needed effort.

Editors, authors, and publishers who are unwilling to have books reviewed here should not send them. Even as one of the lusty siblings of the A. M. A. family of journals we shall try to reach opinions independent of "official" suggestions and policy. The faintest suspicion of response to the long hand of tyranny, the imprint of the stereotype, and the dictatorship of the dull we shall strive to avoid in the tradition of Caesar's wife.

The State of Medicine.—External criticism of medicine usually comes from those who look at things from only one point of view. This is, by definition, the method of bias. This criticism comes to medicine from laymen and politicians who

have some axe to grind or some grievance, real or imagined. Dingle has addressed a searching inquiry into the problem set forth in a scholarly lecture entitled "The Missing Factor in Science." He says: "The history of philosophy in the narrower sense of the word is the history of philosophy, but the history of science is science. Scientific workers may forget this, and knowing little or nothing of the ground on which their edifice rests, may add to its structure and reach positions of the highest eminence in their profession, but they are not educated men." Of knowledge of the history of science they are innocent. They are bricklayers rather than architects. Such uncritical acceptors of the present may accomplish much, but they are potentially dangerous. Lacking judgment, they grow old but not wise. They put all society at risk because they are nourished by illusion. Again he goes on to say "The state of unselfconscious automatism in which science finds itself today is due to the lack throughout its history of a critical school, working within the scientific movement itself, and performing the function or at least one of the functions which criticism has performed for literature from the earliest times."

At least we should begin by remembering Hobbes' admonition of how needful it is "for any man that aspires to true knowledge, to examine the definitions of former authors; and either to correct them when they are negligently set down; or make them for himself." Relatively few of us in the pilgrimage of our scientific speedboats over the high seas of ignorance are aware of how often our direction finder is not dead reckoning but simply dead. With full speed ahead, we often have no sure hand on the rudder. Sometimes we go in circles in a trackless waste. Occasionally we seem to be below water without knowing it. While definitions may not always solve the ambiguity and false representations which lead the unwary to accept a spurious identity of words, ideas, and things, definition will at least help us avoid the facile oversimplification which fails to recognize our problems as beset and influenced by many forces operating simultaneously in complex systems of coordinates. In our understanding of medical problems, we must forever remain alert to the fact that intangible factors must be reckoned, assessed, and measured, for in any patient, as Bridie says, we are "confronted with a concatenation of living, dying, functioning cells, so complicated that it is impossible to understand the simplest of the processes involved . . . concatenations which are influenced arbitrarily by indefinable things called the will and the mind."

A critical forum has provided a wonderful corrective leading to adjustments making it possible to maintain high standards in the fine arts. The quadrennial revolution in our American system of government provides opportunity for political correctives. No such system has existed in medicine.

A critical forum for book reviewing will supply but a part of the requirement. But here at least we can make a start which might lead to further growth of healthy self-criticism in medicine. And healthy criticism need not be constructive, a hopeful, wishful notion of shoring up a rotten superstructure merely by the diagnosis of decay and ruin.

To review medical books as we suggest, hopefully, requires more time and wisdom than we have and more patience and charity than we can expect anyone to muster. Just as medical teaching combines all the difficulties of general teaching with those peculiar to the mixture of medical arts and science, so the reviewing of medical books presents the occupational technical hazards of book reviewing with the innumerable special problems of reviewing medical books aimed to fill diverse needs and to serve many purposes. The central issue is what should be the aim of

reviewing medical books. What is the purpose of a book review? The hazards of book reviewing have been dealt with by Steven Potter in "The Art of Reviewmanship" in his exuberant and keloid style, showing how to get the other fellow in a hole. The essence of gamesmanship is to get the other man down rather than get yourself up. This we shall try to avoid. The real difficulty is getting proper perspective and detachment. E. B. White has summarized the occupational hazards of the critic as follows:

> "The critic leaves at curtainfall
> To find, in starting to review it
> He scarcely saw the play at all
> For watching his reaction to it."

Though the reviewer may be self-conscious, he must not let his preoccupation with the method and manner of reviewing give him only an oil-immersion view of certain sectors or a blurred astigmatic glance rather than a comprehensive and studied perspective. We hope the reviews will be critical, honest, and thoughtful.

In summarizing, our aims are so simple as to be almost impossible to achieve. We hope to avoid spraying mental D. D. T. as self-appointed purifiers. At the same time, we will strive for standards of excellence always somewhat out of reach. Efforts will be made to avoid the implication in the "I-could-have-done-it-better" review. The binding-color-paper-weight-table of contents catalogues we shall minimize but are willing to chastise books without an index or with only an indequate one. References without titles we shall wage war against as we would as upon a publisher's list of books, pamphlets, or papers without titles. Book makers should be reminded of Sir Thomas Browne's annoyance with a "book so long and broad that it becomes untractable and uneasie to make use of." And, finally, unless the divine right of a few typographical errors is abused we will try to follow Oliver Wendell Holmes charitable words to Weir Mitchell—"I have noticed two or three errata which I note for correction in your next edition. . . . It is almost absurd to tail off a letter of acknowledgement with such little specks, but I have read proofs for myself and my friends so often that I am wonderfully dyspeptic of errors such as printers are constantly making."

Such is our purpose—modest but difficult. It will take patience and work. It may be too frustrating a task to get done. But at least we resolve to build up a forum of free opinion about medical books by those who steal time to read, who bother to think, and who are neither ashamed nor afraid to acknowledge it. For the books a man writes and the books a man reads are a measure of the man himself. A man's books, if chosen with thought and taste, become true expressions of his own selection and preference, not those of his book agent or his great uncle.

WILLIAM B. BEAN, M.D.

BOOK REVIEWS

The Vitamins in Internal Medicine. By F. Bicknell and F. Prescott. Third edition. Price, $13.00. Pp. 784, with 245 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

The third edition of Bicknell's text on vitamins is as complete, authentic, and scholarly as its predecessors. To those familiar with the previous editions little more need be added. In this day of the single medical text written often by literally scores of specialists under the editorship of one or two men it is unusual to find a comprehensive text written by two men who have obviously combed the literature of the present and past with thoroughness and who have given the picture as comprehensively and authoritatively as it could be done.

For each vitamin, after a brief history of the steps in the knowledge regarding it, there is a condensed but entirely adequate account of its chemistry, methods of assay, and its absorption, storage, and physiologic effects; blood levels; requirements in animals and man; effects of deprivation and of overdosage, if any; tables showing the sources and approximate quantity in different foods; use in various clinical conditions, and toxic effects, if any. Some idea of the material summarized in the volume may be gained from the fact that there are 5500 references. Yet the book is in no sense a new "review of the literature." The authors speak with considerable candor on controversial topics; consequently, the reader is never uncertain as to their opinions. For instance, p. 657, "Vitamin E is valueless in cardiac diseases. The subject evoked much interest in the later nineteen-forties because the Shute brothers and others claimed that cardiac degenerations, and, especially, angina of effort were greatly improved by massive doses of vitamin E. But all their work is remarkably vague without any controls, and when, rarely, objective findings such as electrocardiographic changes are reported, these again are uncontrolled and indefinite." In the same section the data for and against the value of vitamin E in sterility, habitual abortion, toxemias of pregnancy, muscular dystrophies, degenerative conditions of the spinal cord, peripheral vascular disease, fibroses, and contractures are given factually and fairly.

One is glad that this authoritative book emphasizes the interdependence of the various vitamins upon each other for most efficient absorption and physiologic effect and also the fact that in excess dosage some vitamins, particularly A, D, and *p*-aminobenzoic acid (PABA), may have very harmful effects.

This is no book for easy browsing. It is obvious that the authors have gone at their task seriously and expect concentrated attention from those who dip between its covers. Careful readers will appreciate wise philosophic bits which occasionally shine out from among the scientific detail. For instance, on p. 631, "Nothing is accurately known of the requirements of vitamin E though from the figures given in the preceding table many of the English must consume less than 5 mg. a day yet continue in what in England is regarded as good health. Indeed vitamin E has been considered to be of no importance in human nutrition. But it is fantastic to believe that while mice and monkeys, ducks and dogs, beetles and barrows all need vitamin E, yet a beneficient all wise biological providence has excused man from this irksome necessity. There is also the probability that insufficient vitamin E is one of the reasons why senility pigments or 'metabolic clinkers,' collect in the body's cells over the long course of the years, first to dampen and finally to smother the bright flame of life. It is grievous that our food loses so much of what may be essential protection against senility merely because the vision of science is just as long as the life of a rat."

For those whose vitamin education has for years been from the colorful brochures of the biological houses and the optimistic patter of the detail man, Bicknell's book will be a heartening reversion to the fundamentals.

PAUL S. RHOADS, M.D.

Fluid and Electrolytes in Practice. By Harry Statland, M.D. Price, $5.00. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, 1954.

This is a very general and broad approach to the problems of fluid and electrolyte balance as applied to a wide variety of clinical conditions. The introductory chapters represent a lucid description of the fundamental physical-chemical principles which must be understood before careful consideration can be given the practical aspects of fluid and mineral balance in medical and surgical cases. Considerable discussion is devoted to the physiology of fluid shifts between the various body compartments and the results of these shifts on the concentration of the principle electrolytes—sodium, potassium, and chloride ions. Particular emphasis is placed on the effects of various types of dehydration on the distribution of fluid and electrolytes within the body. After development of these clinical-physiological principles, attention is given to their relationship to the regulation of acid-base balance. A discussion of the etiology and differentiation of the various types of disturbances in acid-base balance is also given.

The above discussions are not exhaustive but are intended for use by clinicians who are not specialists in this area of clinical physiology. However, the reader may gain considerable insight into the fundamental aspects of fluid balance if the various sections are read carefully. The author has employed a very lucid style throughout.

The second half of this book deals specifically with various clinical conditions such as cardiac disorders, burns, renal disease, diarrheas, etc. Here, by the use of actual case presentation, the use of the knowledge gained from the first half of the book is illustrated.

It is my opinion that this book, while too elementary for the student or specialist, will serve as a useful guide for the medical or surgical practitioner. Of particular value are the many "rules of thumb" given together with their rationale.

EARL T. CARTER, M.D.

Differential Diagnosis: The Interpretation of Clinical Evidence. By Harvey and Bordley. Price, $11.00. Pp. 665. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

I am glad I read the text of this book before reading the introduction. I formed the opinion that the book reflected much more than just the contributions of Harvey and Bordley—that it was, in fact, the embodiment of work done in the great clinical tradition of William Osler, handed down through Thayer, Barker, Hamman, and Longcope to the authors. The introduction demonstrates this as the purpose and the method. This book in a way develops the history of clinical medicine as it evolved at the Johns Hopkins Hospital and Medical School. But in a larger sense it exemplifies certain characteristically American features ot clinical teaching, emphasizing the clinical pathological conference and teaching at the bedside. This book plays on varying themes—the clinical history, clinical examination, laboratory examinations, the narrative of the course of a disease, and the final exposition by the pathologist of the findings at autopsy. The profound influence of Hamman and Longcope I note particularly. I knew them both well when I was an intern, during the period when Bordley was chief resident and Harvey a junior assistant resident.

This book will be very helpful and instructive to any physician who takes the time to analyze each case presented after he has read the introductory chapter dealing with the types of problems to be illustrated. Only those with strong forebearance will be able to avoid jumping ahead occasionally, as with a detective story, to get the answer to the question "Who-dun-it?" This book differs from the ordinary crossword puzzle book because it remains a valuable reference book for review when puzzling cases are encountered after it has been studied. For those who are too impatient to refrain from looking at the end of the page, the last chapter of the book contains a series of unknowns with the ultimate findings hidden in a separate section of the book. Fortunately, this book has an excellent index. It would lose all value as a reference book without one. While it does not pretend to be an encyclopedia, it certainly includes the vast majority of situations which present diagnostic difficulties. It is not, as so many treatises become, just a repository of rare diseases or rare aspects of common diseases. Emphasis on the important body systems and their important diseases gives a well-rounded perspective. The inclusion of more surgical cases would have enhanced the book's teaching and reference value.

If one wished to find a fault, one could complain that the references are somewhat inadequate. It may thereby lose some interest for the medical scholar. A tendency to quote home-grown material must be accepted because of the intensely individual and personal nature of this book, a value it might lose if it had aimed at a more universal scope. Still, classical articles should be included and one misses reference to Soma Weiss' papers on neurological defects of lymphomas, Carter and Giuseffi's papers on strangulation of post-traumatic diaphragmatic hernia. Every critic must ventilate some ire, and I exercise my prerogative in a gentle lament over the use of that outmoded solecism of our neurological brothers "space occupying lesion." Even a biochemical lesion occupies space and if an expanding lesion is meant, why not say so. Tut! Tut!

As with all useful clinical books, the view here is retrospective. Clinical medicine is born of experience, and a clinician who sees many patients and sees them perceptively mellows with age as does good wine, which this book clearly shows. Altogether, it reflects enough credit upon the authors for some to spill over onto the Johns Hopkins School of Medicine and Hospital as worthy representations of American medicine.

WILLIAM B. BEAN, M.D.

The Cerebrospinal Fluid. By S. Lups, M.D., and A. M. F. H. Haan, M.D. Price, $9.50. Pp. 350. Elsevier Press, Inc., 402 Lovett Blvd., Houston 6, Texas, 1954.

This is the first book regarding the cerebrospinal fluid to be published in English since Merritt and Fremont-Smith's volume appeared in 1937. Lups and Haan's work would accordingly be of value for this if for no other reason.

It is regrettable that the translation tends to be literal and as such lacks felicity. In some instances the awkwardness of expression and quaint terminology serve to confuse, although this is exceptional. It is surprising, for example, to read (following a proper description of the aim

of Queckenstedt's maneuver): "It is also possible in this way to diagnose tumors of the fossa cerebellaris." While the statement is undoubtedly correct, the use of the procedure in the presence of a neoplasm of the posterior fossa is so manifestly incorrect that the inclusion of the statement is unwarranted.

The book is well-planned, and anatomic, physiologic, clinical, and technical topics are dealt with in a thorough but occasionally repetitious fashion. Many laboratory procedures which are not in common use in this country are considered in detail, and this is a useful feature. Certain recent developments, however, are not included, e. g., the relation of CSF gamma globulin values to disorders of the nervous system.

The bibliography is extensive and contains a preponderance of European references—another good feature for the American reader. The index is adequate. The book is recommended for clinical or reference purposes.

TIFFANY LAWYER, M.D.

Clinical Biochemistry. By Abraham Cantarow, M.D., and Max Trumper, Ph.D. Fifth edition. Price, $9.00. Pp. 738, with 54 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

The publication of the fifth edition of this familiar text indicates not only the growing scope and importance of clinical chemistry, but also that the authors have kept their book abreast of the new developments.

The present volume opens with a discussion of carbohydrate metabolism which is more general and more detailed than in the past. By a dynamic biochemical approach and by frequent cross references to material in later chapters the concept of a common final metabolic pathway is firmly established. Significant new research is described with a nice balance between bewildering detail and vague generalities. The central role of coenzyme A and the "two-carbon fragment" is described first as a general metabolic principle and then as a mechanism responsible for such situations as the hypercholesterolemia of diabetes, etc. The glucagon-insulin system is compared with and also differentiated from the epinephrine-insulin system. Much of the clinical material on diabetes, previously presented separately, is now included in this chapter.

The discussion of the lipids is also patterned on the basis of metabolic interrelationships, and it has been enlarged to include a short section on the complexes of lipids with proteins. A brief survey of bile acid metabolism is another worth-while addition.

The chemistry of the proteins is examined from the metabolic and nutritional viewpoints. New material has been added covering the effect of steroid hormones on nitrogen retention in disease and in therapy. Interpretation of serum and plasma levels has been related to chemical methodology, including electrophoresis, and the discussion includes some excellent cautionary notes. Surprisingly, no mention is made of commonly employed methods based on the work of Cohn and Wolfson. The material on nucleoproteins as catalysts and as structural elements has been expanded and gathered together and is for the first time given chapter status. The same treatment is accorded to hemoglobin and the porphyrins, although the discussion is disappointingly brief.

The next ten chapters form a unit dealing with the metabolism of inorganic substances. Calcium and phosphorus, discussed under a single heading, are treated in a somewhat synoptic manner. This is followed by a chapter on the phosphatases as parameters of disease. Successive chapters review sulfur, magnesium, iodine, and iron metabolism. More might have been made of the chapter on iron, but the others are adequate. The remainder of this section is devoted to the metabolism of sodium, potassium, chloride, and water metabolism and a discussion of neutrality regulation. The authors have deliberately phrased their review in general terms and have avoided specific examples. Cross references to these related chapters are a little sparse, and the important topic of repair and replacement therapy is unfortunately not discussed. A concise but thorough description of chemical control of respiratory mechanisms concludes this unit.

The chapter on hormone assay and endocrine function has been completely rewritten and is nearly doubled in size. Both chemical and bioassay procedures are reviewed, and the different results in the two types of tests are examined. The section on techniques applicable to clinical endocrine studies should be of value to many clinicians. New material on the chemical evaluation of adrenomedullary disease is included, and extensive cross references to other sections of the book emphasize the multiple manifestations of endocrine disturbances.

One of the outstanding contributions of this book is the section on function studies of the stomach, pancreas, liver, and kidney. Approximately the last quarter of the text is devoted to a review of these subjects. The revisions include a discussion of "tubeless gastric analysis" and its evaluation as a diagnostic tool. The discussion of the value of fecal fat studies in pancreatic disease is especially pertinent. Differential diagnosis of liver diseases by function studies is excellently covered, and the folly of undue reliance on chemical studies is made quite plain. The chapter on renal function has been strengthened by inclusion of more basic physiology and by a more detailed analysis of various clearance measurements. The information on localization of renal defects has been covered in a particularly comprehensible manner.

The over-all utility of the book has been increased in other ways. The index has been revised and expanded by almost twenty per cent. The previous bibliography of specific citations has been replaced by a listing of more general authoritative review articles, many as recent as 1954. Functional use of subchapter headings and outline summaries of important topics will endear the style of presentation to anxious students and busy practitioners alike. A clean type on excellent paper add to the readability of the volume, which has been handsomely produced. This book should give aid and comfort to anyone seeking an increased understanding of biochemistry as it relates to medicine.

R. L. DRYER, M.D.

Surgical Forum, 1954: Proceedings of the Forum Sessions, Fortieth Clinical Congress of the American College of Surgeons. Price, $10.00. Pp. 851, illustrated. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

Each year since 1941 The American College of Surgeons has held a Forum on fundamental surgical problems, which was originated under the guidance of Owen H. Wangensteen. Since 1951 the collected papers from this meeting have been published annually. In this latest volume there are 154 papers, presented in 10 different sections. Each section is introduced by an authority in the field, who summarizes and evaluates the papers presented. Approximately one-third of the papers are concerned with research in the related fields of heart and vascular surgery. Another one-third of the papers are devoted to investigations of nutrition, body fluids, metabolism, steroids, and cancer. The remainder are related to the gastrointestinal tract, liver and pancreas, anesthesiology, burns, shock and wounds, and use of plastics.

This volume previews much of what will appear in the literature and in greater detail during the ensuing year. If there are those who believe that specialization is currently a dangerous trend they would do well to read this volume. The work being done today in our medical research centers cuts across many boundaries, and there is evident a healthy attitude of pursuing problems without regard for the complexity or derivation of the tools required.

E. E. MASON, M.D.

Pathology for the Surgeon. By William Boyd, M.D. Seventh edition. Price, $12.50. Pp. 737, with 547 illustrations, including 10 in color. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

This is the seventh edition of the book originally published as "Surgical Pathology." The author not only has changed the title but has rewritten the text. The contents, organization, and format are excellent. The illustrations are improved over those of previous editions. Dr. Boyd has directed the volume at the graduate student and has therefore emphasized clinical and practical aspects of surgical diseases. He has brought the material up to date and has included many new features not present previously in his volume "Surgical Pathology." Each chapter has a table of contents, and a well-chosen bibliography is presented at the close of each chapter. In this text discussions of pathologic physiology as well as the relation of symptoms to lesions are found.

The text will not only be of benefit to the surgeon but will prove of interest and convey considerable information to the internist. The latter is well acquainted with the author's informative volume "The Pathology of Internal Diseases." This is as well written and is full of interesting quotations, as exemplified by this passage taken from John Hunter, "The last part of surgery, namely operation, is a reflection on the healing art; it is a tacit acknowledgement of the insufficiency of surgery. It is like an armed savage who attempts to get that by force which a

civilized man would get by stratagem," or the following, as important today as when written by Velpeau in 1856, "To destroy a cancerous tumor by surgical means is usually an easy matter and but little dangerous in itself, but the question arises whether such a proceeding affords a chance of radically curing the patient."

The volume is strongly recommended not only for the surgeon but for those practicing in other fields as well.

SIDNEY ZIFFRIN, M.D.

Handbook of Treatment. By Harold Thomas Hyman, M.D. Price, $8.00. Pp. 511. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, 1955.

For those who like their medical knowledge in the form of a dictionary, this book will serve the purpose well. It covers the management of symptoms and syndromes as well as disease entities and contains brief but effective comments on the comparative value of the large variety of drugs now available. The discussion of each topic begins with general principles, then deals with immediate care and continuing care of the patient. There are also remarks on prophylaxis, diagnostic tests, contraindications to the use of drugs or hormones, and other interesting comments. While the text is necessarily highly condensed, there is a striking amount of useful and accurate information for the physician who wants more than the name and the dose of the drug for a given condition. The author manifests a healthy skepticism in regard to the ineffective drugs but is somewhat inclined to overemphasize the newest preparations by using such terms as "extraordinarily effective," for example, in the case of the anticholinergic drugs. On the whole, the book should prove very useful to the busy physician and may prove as a stimulus to deeper reading, since there are references to the literature in the text.

LOUIS LEITER, M.D.

Transactions of the Fourteenth Conference on the Chemotherapy of Tuberculosis by the Veterans Administration, Army and Navy, with the Cooperation of the National Tuberculosis Association, Feb. 7 to 10, 1955. Price, given on request only. Pp. 556, with many graphs, tables, and illustrations. Veterans Administration, Washington, D. C., 1955.

This paper-bound volume contains a faithful reproduction of about sixty papers plus informal discussion and comments pertaining to them. Another thirty papers "Read by Title" are included. Full committee reports are given, dealing primarily with future plans in this continuing cooperative study (now in its tenth year), covering tuberculosis therapy in Army, Navy, and Veterans Administration hospitals. The grouping of papers is as follows: Pulmonary Tuberculosis; Extrapulmonary Tuberculosis; Laboratory; More General Matters; New and Recent Drugs.

By review of the results of nine years of continuous study of large groups of patients and reports on more recent observations, the field of drug therapy for tuberculosis is well covered. In addition, other forms of therapy are evaluated; other pulmonary diseases, particularly the mycoses, are discussed, and some references are made to relationships between antituberculosis drugs and other diseases.

The transactions tend to indicate that single drug treatment is less effective, mainly because of greater incidence of acquired drug resistance by tubercle bacilli; that a regimen of isoniazid and aminosalicylic acid (PAS) is slightly superior to streptomycin-PAS or streptomycin-isoniazid regimens; that there is no good reason to use all three of these drugs in combination, except possibly in tuberculous meningitis; that pyrazinamide with isoniazid makes an effective combination, but the former possesses considerable potential for hepatotoxicity; that very prolonged courses of drug treatment are advantageous. One potentially valuable new drug was announced—Cycloserine.

The problem of residual necrotic foci or actual cavitary lesions containing seemingly nonviable bacilli, and the need for resection of such lesions, remains a major and unanswered one.

The work is lengthy but invaluable for the physician managing tuberculous patients and is perhaps the outstanding reference on current management of tuberculosis in this period of extremely rapid therapeutic evolution. It is fully indexed.

CHARLES W. GRAY, M.D.

A Textbook of Medicine. By R. L. Cecil and R. F. Loeb. Price, $15.00. W. B. Saunders Company, 216 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

This book continues to be the outstanding single volume on the medical diseases. The contributors are authorities in the field, although there is a tendency for some of the contributors to write about diseases which they have observed little personally, if at all. It would appear more desirable to have the diseases reviewed by physicians fully experienced with the clinical problems whenever possible. Perhaps convenience has prompted the selection of contributors, since they had already contributed to other aspects of the same field or related diseases.

The format and presentations in this edition are essentially the same as for the previous editions. The discussions are brought up to date. In fact, the various editions of this fine book on medicine trace well the history of internal medicine for more than the past two decades. Although the discussion may be considered by some to be too detailed for undergraduate students of medicine, it remains a good and reliable source of information on many diseases of man. It can be highly recommended for all students of medicine, including practicing physicians. It should serve as a valuable reference book and should be available on every doctor's book shelf for rapid reference to many of his problems. It cannot replace the original contributions found in the literature and surely is not intended to do so. As a supplement to the journals in medicine, however, this book has served and should continue to serve a useful purpose. Its price reflects the economic status of our times and the value of the American dollar.

GEORGE E. BURCH, M.D.

News and Comment

ANNOUNCEMENTS

New Appointments.—Appointment of ten members to the newly established National Advisory Allergy and Infectious Diseases Council was announced today by Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare.

The Council has been set up to facilitate activities of the new National Institute of Allergy and Infectious Diseases. This Institute, redesigned from the former National Microbiological Institute, has been established to provide for expanded studies on allergy and to meet the growing needs on infectious disease research. The Institute of Allergy and Infectious Diseases is one of the seven National Institutes of Health which comprise the principal research branch of the Public Health Service.

Upon recommendations of the Council, the Surgeon General will award grants to scientists in universities and other nonfederal institutions for research on allergy and infectious diseases. The Council will also assist in providing guidance on broad research policies related to the programs of the National Institute of Allergy and Infectious Diseases. Members of the Council are leaders in science, education, and public affairs. The Council will hold its first meeting March 7 and 8, at the National Institutes of Health in Bethesda, Md.

At present two vacancies remain on the Council. These are expected to be filled in the near future.

The members are as follows: Dr. René J. Dubos, member of the Rockefeller Institute for Medical Research, New York; Dr. Karl F. Meyer, Director of the G. W. Hooper Foundation, University of California Medical Center, San Francisco; Dr. Gail M. Dack, Director of the Food Research Institute, University of Chicago; Dr. Edwin B. Fred, President of the University of Wisconsin, Madison; Dr. Charles E. Smith, Dean of the School of Public Health, University of California, Berkeley; Dr. H. O. Halvorson, Head of the Department of Bacteriology, University of Illinois; Mr. Byron H. Larabee, President of Firestone Plantations Company, Akron, Ohio; Mr. David C. Crockett, Associate Director, Massachusetts General Hospital, Boston; Mrs. Rollin Brown, of Los Angeles, President of the National Congress of Parents and Teachers; Mr. John Abbink, of New York, President of the American Foundation for Tropical Medicine.

Student Research Fellowships.—Medical Student Research Fellowships, available to medical schools throughout the United States and Canada, are now being offered for the current year by Lederle Laboratories Division, American Cyanamid Company.

The Fellowships, not exceeding $600 for any one person, are intended to relieve some of the financial burden of students who desire to devote their summer vacations to basic research in the preclinical medical sciences.

Selection of students to receive the award will be made by the dean of the medical school or his selection committee. Students who apply must be of good scholastic standing and have the consent of the faculty member under whose supervision their research is to be conducted. Such research may be carried on in another medical school if the arrangements are satisfactory to faculty authorities in both schools.

American Public Health Association Meeting.—The American Public Health Association announces that the 84th Annual Meeting of the Association and meetings of 40 related organizations will be held in Convention Hall, Atlantic City, N. J., Nov. 12 to 16.

The explorations into the important question, "Where Are We Going in Public Health?", which were undertaken at the 83d Annual Meeting last November, will be continued. The 13 Sections of the Association, namely, Dental Health, Engineering and Sanitation, Epidemiology, Food and Nutrition, Health Officers, Laboratory, Maternal and Child Health, Medical Care, Occupational Health, Public Health Education, Public Health Nursing, School Health, and Statistics have been augmented this year by a new Section on Mental Health. Each will be responsible for programs in its specialties.

Grants for Leukemia Research.—The trustees of the Leukemia Society, Inc., are offering during 1956 grants-in-aid to qualified investigators to support research projects on leukemia.

The Society will also accept applications for fellowships for studies in the field of leukemia and allied diseases, to be given during the year 1956-1957.

Dr. Herbert C. Lichtman, Assistant Professor of Medicine and Head of the Hematology Division, State University of New York, Brooklyn, is Chairman of the Selection Committee which reviews applications from North America.

Public Health Service Awards.—The Public Health Service awarded 3036 research grants totaling $36,522,408 between July 1, 1955, and Jan. 1, 1956, from fiscal year 1956 funds appropriated to the National Institutes of Health, the PHS research bureau at Bethesda, Md. The grants will aid research in medical schools, hospitals, and other non-Federal institutions throughout the country.

Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare, today relased a summary of research grants he approved for payment during the first half of the current fiscal year. These support medical research on all major diseases and in basic sciences related to medicine. Institutions receiving the grants number 350 and are located in 46 states, the District of Columbia, 2 Territories, and 7 foreign countries.

About 95% of the research grant funds for the current fiscal year have been committed.

Of the 3036 grants, 634 were new—that is, awarded for the first time. The remaining 2402 were continuation grants, supporting studies that had received similar funds during the previous year.

The awards were made following recommendations of the National Advisory Councils at meetings in Bethesda during March, June, and October, 1955. The seven councils are each composed of twelve non-Federal experts in medical science or public affairs, with ex officio members from the Department of Defense and the Veterans' Administration. The groups meet three times a year to advise the Surgeon General on grant applications and other matters concerning the Institutes.

A tabulation of the awards follows:

Granting Organization	No. of Grants	Total
Institute of Arthritis & Metabolic Diseases	87 (new) 342 (cont.)	$4,620,298
Institute of Neurological Diseases & Blindness	78 (new) 327 (cont.)	4,274,424
Cancer Institute	64 (new) 564 (cont.)	8,346,815
Institute of Allergy & Infectious Diseases	86 (new) 121 (cont.)	2,110,000
Institute of Dental Research	5 (new) 44 (cont.)	421,000
Heart Institute	139 (new) 566 (cont.)	8,420,936
Institute of Mental Health	42 (new) 139 (cont.)	3,828,935
Division of Research Grants	133 (new) 299 (cont.)	4,500,000
Total	634 (new) 2,402 (cont.)	$36,522,408

Of the above awards, 1991, in the amount of $22,934,811, became active during the six-month period. The remaining grants will have become active by July 1, 1956.

Further information on the 1991 activated grants, such as name of investigator, institution, and amount of support, may be obtained from Office of Medical Research Information, National Institutes of Health, Bethesda 14, Md. Telephone OLiver 6-4000, extension 849.

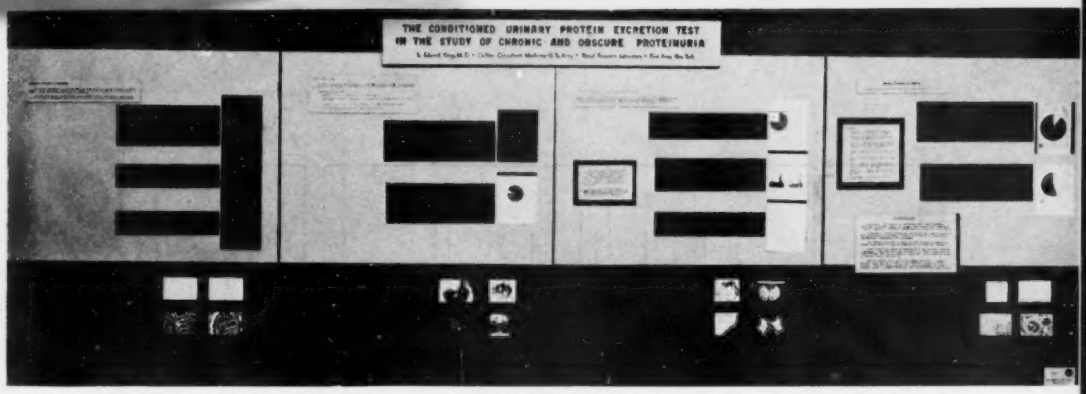
Pediatric Courses.—The following short courses will be conducted at The Children's Hospital of Philadelphia in May and June, 1956.

1. Pediatric Advances for Pediatricians and General Practitioners. May 28 through June 1, 1956. A Refresher Course conducted by the Staff of the Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Camden Municipal Hospital. Tuition, $100.00.

2. Practical Pediatric Hematology. June 4, 5, and 6. Conducted by Dr. Irving J. Wolman and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $60.00.

3. Blood Group Incompatibilities and Erythroblastosis Fetalis. June 7 and 8. Conducted by Dr. Thomas R. Boggs Jr., of the Philadelphia Serum Exchange of the Children's Hospital of Philadelphia, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $50.00.

For information write to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46.



Scientific Exhibits

THE CONDITIONED URINARY PROTEIN EXCRETION TEST IN THE STUDY OF CHRONIC AND OBSCURE PROTEINURIA

S. EDWARD KING, M.D.
New York

INTRODUCTION TO EXHIBIT

THIS REPORT covers a study of over four years' duration of approximately 4500 young males, referred to U. S. Army Hospital, Fort Jay, N. Y., because of proteinuria. Experiences with the urinary protein excretion test have been previously reported.[1,4,5]

The evaluation of renal disease through observed alterations in urinary protein excretion with postural change and activity is not a new concept. [6,7] The necessity for accurate urine collections, to assure that specimens correctly represent specific periods, has not been emphasized. Pooling of specimens and dilution are common sources of error. Although most patients will follow suitable instructions, there is a stubborn minority requiring close supervision. Clearly defined standards of interpretation, with rejection of noninterpretable tests, repeated as required, yield reliable results that can be duplicated in approximately 95% of cases.

Considerable collateral information has been developed in this study. Prevalent concepts concerning orthostatic proteinuria require revision. Persistent orthostatic-type proteinuria indicates early or latent but not necessarily static lesions in various renal diseases of different tempo and course.

That latent nephritis, early pyelonephritis, and renal vascular disease may be manifest only by apparently innocuous orthostatic proteinuria is restatement of known clinical facts. Experiences suggest that these facts are not generally recognized.

Prevalent confusion concerning this subject is due to lack of clear definition of the various types of proteinuria. The pattern of protein excretion may serve in differentiation and study of the course and evolution of cases of obscure chronic proteinuria.

Intermittent proteinuria is a functional manifestation of unstable neurocirculatory homeostasis. Little is known concerning its course. The experimental production

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The Renal Research Laboratory, First Army.

The Armed Forces Institute of Pathology, Washington, D. C., gave technical assistance in preparation of this exhibit.

of proteinuria in man with intravenous adrenal medullary amines [2,3] may contribute to elucidation of some of the mechanisms of proteinuria.

Certain limitations in these clinical data are evident. Severer and more persistent cases of proteinuria were selected by dispensaries and examining stations for hospital study. Limited periods of observation often excluded desirable procedures. Urologic study was rarely possible, and intravenous urography was obtained in only several hundred cases. Even within such limits, general conclusions are clear and uneqivocal.

There is scant knowledge and many misconceptions are prevalent concerning very common disorders, which may be related to renal and vascular disease of later life. It is a striking commentary on the present status of diagnosis in this field that most cases of advanced renal disease in the young persons in this study were discovered accidentally, some when renal insufficiency was imminent.

PATHOLOGIC PHYSIOLOGY OF PROTEINURIA

Proteinuria (albuminuria) is derived from serum proteins excreted by the kidneys or postrenal exudate. Renal proteinuria indicates kidney injury; its pattern of excretion is controlled by kidney function and is predictable under set conditions.

The body fluid balance through urinary volume inversely affects urine protein concentration but not the rate of excretion. Small quantities of protein may escape detection in dilute urines.

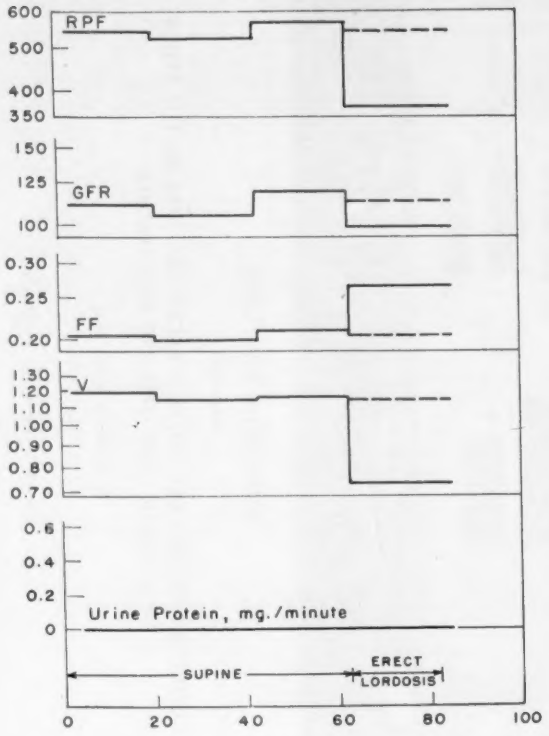
Postural Renal Ischemia

Renal plasma flow, glomerular filtration and urine volume fall in normal man on standing.

Intermittent Proteinuria

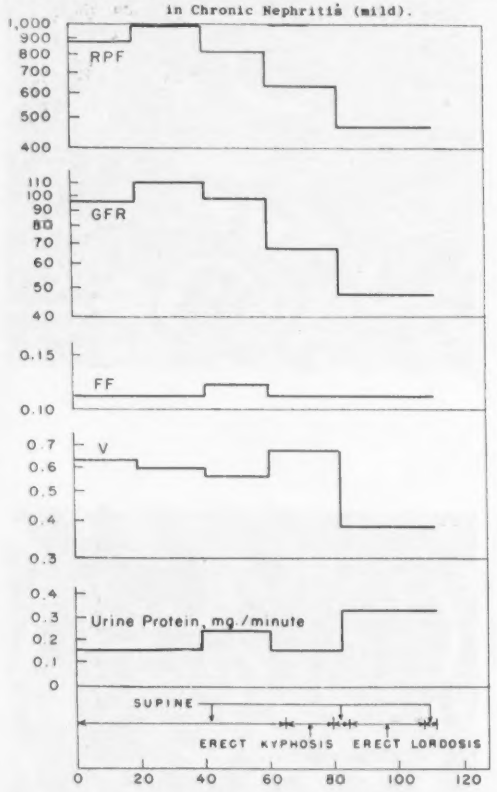
Prolonged standing and stress conditions in some persons are followed by weakness and hypotension, associated with marked reduction in renal plasma flow and transient proteinuria.[1] Proteinuria follows renal ischemia regularly induced in man by intravenous arterenol (Nor-Epinephrine) and epinephrine.[2,3]

The Effect of Posture upon Renal Function in Normal Man.



Upon change from supine position to erect lordosis there occurs a reduction in renal blood flow (RPF), glomerular filtration rate (GFR) and urine volume without proteinuria. The magnitude of these alterations may be similar to that occuring in Orthostatic Proteinuria.

The Effect of Posture upon Renal Functions and Protein Excretion in Chronic Nephritis (mild).



Upon assuming the erect position there occurs a fall in renal plasma flow (RPF) and glomerular filtration rate (GFR) and urine volume. Protein excretion is moderately increased in erect lordosis. This effect has been partially masked by the unusual fall of GFR in this instance.

Orthostatic Proteinuria

(Postural Renal Ischemia and Renal Lesions)

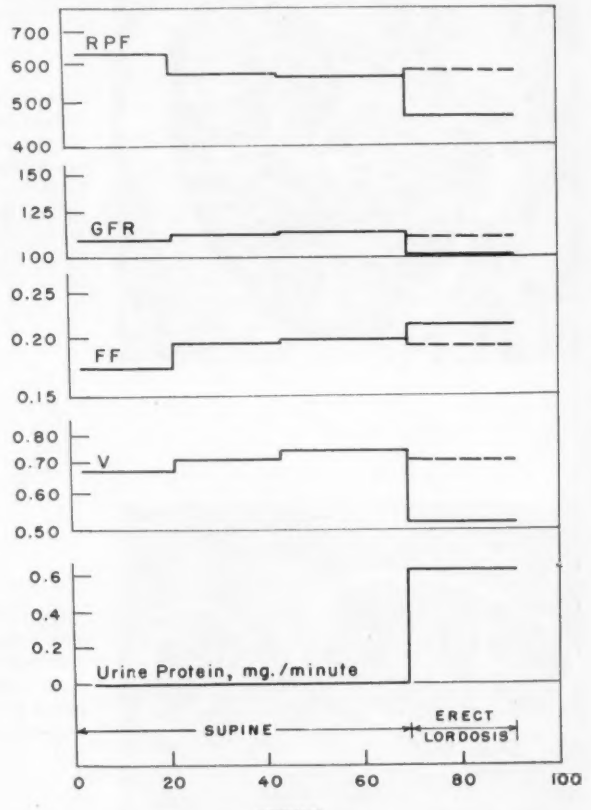
Frequently, in the healing stage of glomerulonephritis, protein excretion is increased on standing.

Later, proteinuria may appear in such patients only on standing. "Orthostatic proteinuria" following glomerulonephritis may persist indefinitely.

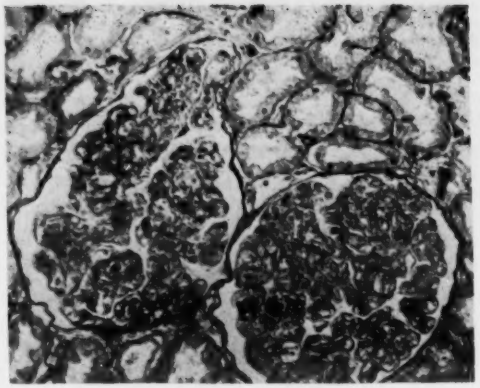
In subjects with "orthostatic proteinuria" normal renal postural alterations are associated with proteinuria and at times with mild sediment abnormalities.

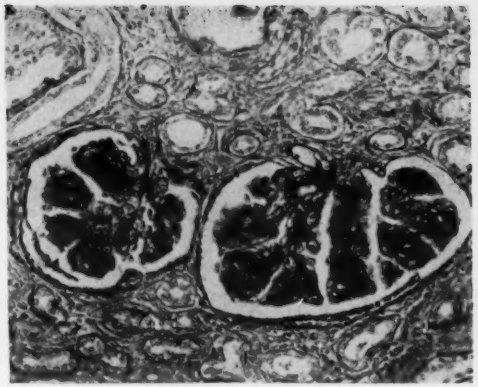
Careful study of subjects with "orthostatic proteinuria" may elicite history or evidence of acquired or congenital renal pathologic lesions.

The Effect of Posture upon Renal Function in Orthostatic Proteinuria



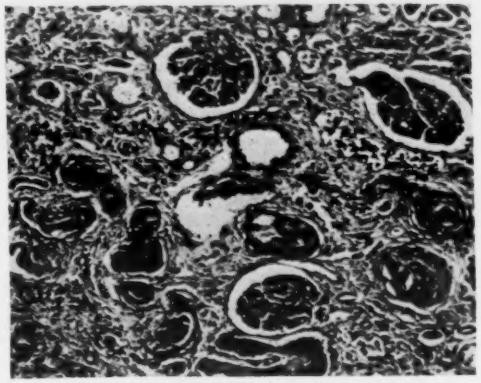
Upon changes from the supine position to erect lordosis there occurs a reduction in renal blood flow (RPF), glomerular filtration (GFR) and urine volume with moderate proteinuria. These alterations are similar to those in normal man.

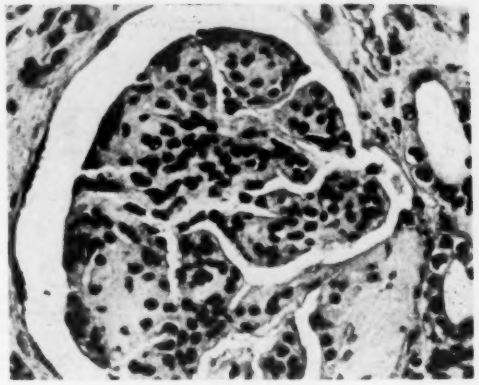




Nephritis

Orthostatic type proteinuria may follow apparent recovery from acute nephritis (left) and may persist for decades. It also follows focal and diffuse renal lesions associated with various infections and toxic agents and has been observed after remission from "nephrosis" (chronic membranous nephritis) (right).





Renal Vascular Disease

Renal arteriolosclerosis with benign hypertension (left) is frequently manifested by proteinuria of the orthostatic type. Proteinuria in vascular diseases of the kidneys including diabetic glomerulosclerosis (right) and amyloid and collagen diseases denotes progressive renal pathology and is not benign. With advanced renal disease proteinuria becomes continuous.

CLINICAL APPLICATIONS

Variable proteinuria of obscure origin is a very common clinical finding. Failure to distinguish between various types of proteinuria and inadequate methods of study have contributed to confusion in this field.

Suggested Classification:

1. Transient (accidental) proteinuria (not significant).
2. Intermittent (recurrent) proteinuria (an exaggerated functional reaction to stress and posture).
3. Orthostatic proteinuria (a chronic disorder indicating covert renal disease).
4. Continuous proteinuria (moderately advanced renal disease).

The Conditioned Serial Urine Protein Excretion Test

The procedure was developed to minimize errors and increase sensitivity of protein detection. Basic concepts, procedure, and results have been reported previously.[1,4] Properly controlled conditions are essential for reliable results. Three standard patterns of protein excretion are possible:

1. Constant (continuous)
2. Inconstant (orthostatic)
3. Negative

Irregular patterns indicate postrenal proteinuria or inaccurate urine collections.

URINARY PROTEIN PATTERNS
(SCHEMATIC)

URINE SPECIMEN	A CONSTANT	B NEGATIVE	C (ORTHOSTATIC)	D IRREGULAR
1	+	-	+	+
2	+	-	-	- +
3	+	-	-	+ -
4	+	-	+	+
5	+	-	+	+

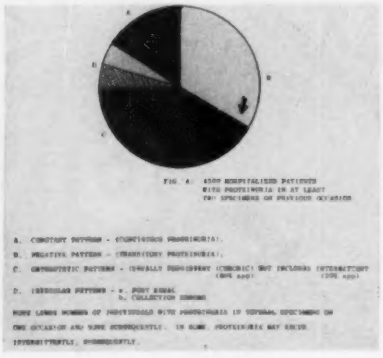


FIG. 4. 4500 HOSPITALIZED PATIENTS
WITH PROTEINURIA IN AT LEAST
TWO SPECIMENS OF PREVIOUS EXCRETION

A. CONSTANT PATTERN - (CONTINUOUS PROTEINURIA).

B. NEGATIVE PATTERN - (TRANSITORY PROTEINURIA).

C. ORTHOSTATIC PATTERN - (USUALLY BENIGN) (CHRONIC) BUT INCLUDES INTERMITTENT (30% ADD) (20% ADD)

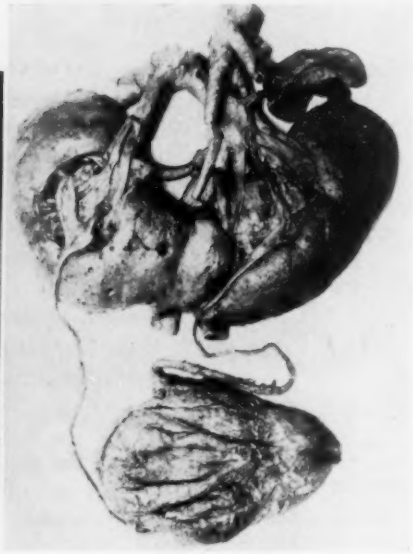
D. IRREGULAR PATTERN - e. POST RENAL
b. COLLECTION ERRORS

MORE LARGE NUMBER OF INDIVIDUALS WITH PROTEINURIA IN SEVERAL SPECIMENS ON ONE OCCASION AND NONE SUBSEQUENTLY. IN SOME, PROTEINURIA MAY RECUR INTERMITTENTLY, SUBSEQUENTLY.

RESULTS: Results with this test in approximately 4500 hospitalized subjects are summarized.

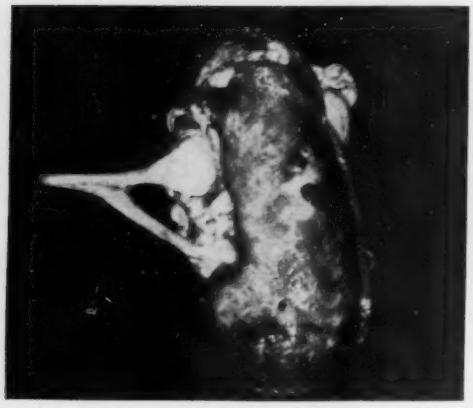
This procedure is not a substitute for individual clinical study. Over short periods, patterns have proved very consistent. If the test is properly performed and interpreted, an accurate pattern can be obtained in 95% of cases. As with other renal-function tests, protein-excretion patterns vary with change in underlying renal disease.

In doubtful cases the test determines the necessity for further detailed study and serves as a point of reference for periodic observation. The relative incidence of patterns in this selected hospital group is indicated.



CONGENITAL RENAL ANOMALIES

Ectopic kidneys (left) and fused (horseshoe) kidneys (right) are prone to infection and calculus formation. Variable proteinuria, pyuria, and hematuria are frequent.



CONGENITAL RENAL ANOMALIES

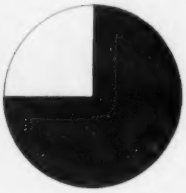
Although occurring so frequently that it is sometimes considered a normal variation, reduplication of renal pelvis and ureters (left) apparently predisposes to infection and calculus. Orthostatic and irregular proteinuria and recurrent hematuria are common.

Proteinuria is frequent with hypoplastic kidney (right).

ORTHOSTATIC PROTEINURIA—NATURE, SIGNIFICANCE, AND COURSE

This disorder is associated with a variety of renal lesions, including diffuse and focal glomerulonephritis, congenital renal anomalies, chronic pyelonephritis, and renal vascular diseases. Many of these conditions are latent; others are active and progressive. Common misconceptions about this disorder are discussed.

PERSISTENCY OF ORTHOSTATIC PROTEINURIA



SHADED AREA = PERSISTENT

170 CASES
FOLLOWED UP TO 3 YEARS BY
CONDITIONED PROTEIN
EXCRETION TEST

PROTEINURIA PERSISTENT } 130/170 = 76%

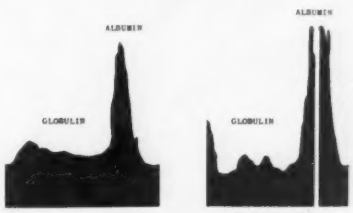
Orthostatic proteinuria is a persistent (chronic) condition. It is not a benign disorder which always tends to disappear in later life.

Significantly active renal lesions may be manifest in many patients with orthostatic type proteinuria, as indicated by

1. Intense proteinuria (rates often 1 mg/minute, sometimes much higher, comparable with that in nephritis or nephrosis).
2. Protein may be present in most day specimens.
3. Globulinuria may be marked (see Figure).
4. Sediment abnormalities may be observed in fresh specimens.

Although frequently dismissed as inconsequential, these cases represent active Bright's disease.

ELECTROPHORETIC PATTERNS OF URINE PROTEINS IN ORTHOSTATIS PROTEINURIA



ANALYSIS OF THE URINE PROTEINS IN TWO ILLUSTRATIVE CASES WITH ORTHOSTATIC PROTEINURIA BY THE TISELIUS MOVING BOUNDARY METHOD REVEALS CONSIDERABLE GLOBULIN IN THE ALPHA, BETA AND GAMMA FRACTIONS.

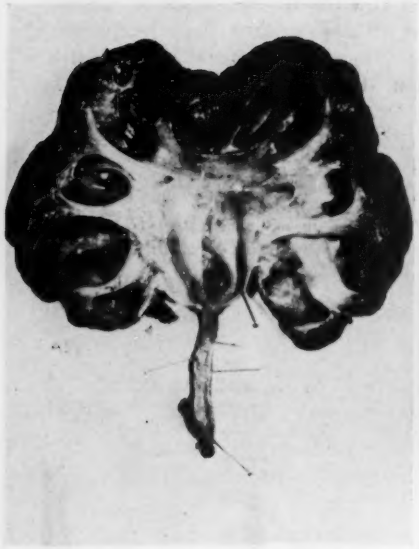
INCIDENCE OF CONGENITAL RENAL ANOMALIES IN SUBJECTS WITH ORTHOSTATIC PROTEINURIA

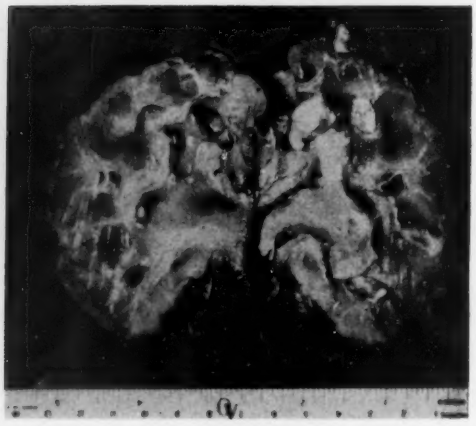
110 Consecutive cases. Studied by Intravenous Urography

Congenital renal anomalies are not the commonest cause of this disorder and are demonstrable by clinical methods in only a minority of instances. Congenital (or acquired) abnormalities of kidney or urinary tract, however, favor infection and progressive renal destruction. They cannot be considered benign. Early diagnosis and treatment may prevent serious renal disability.

Renal pathologic lesions may be demonstrated in many subjects with orthostatic proteinuria. Particular attention is called to chronic pyelonephritis, which is common and of insidious and progressive course. Proteinuria and pyuria are frequently inconstant. Diagnosis of pyelonephritis at an early stage may be extremely difficult, but it is essential to avoid eventual renal destruction.

Life insurance experiences suggest a higher delayed mortality from diseases of the kidney, heart, and blood vessels in persons with inconstant proteinuria even of mild degree (Excess Mortality=150%±6).[8]





URINARY TRACT OBSTRUCTION AND CALCULUS

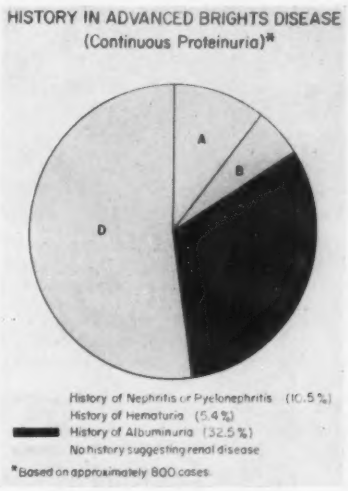
Acquired or congenital obstructive lesions of the urinary tract produce stasis with infection and calculus. Orthostatic and irregular proteinuria are practically invariable and are frequently the presenting finding. Partial pelvic obstruction may be due to aberrant vessels (left). Giant staghorn calculus (right) may be discovered solely because of irregular proteinuria.

URINARY TRACT OBSTRUCTION

With marked pelvic obstruction (left) and ureteral obstruction due to stone or stricture, acquired or congenital (right), parenchymal destruction gradually develops. Proteinuria of all types may be found, depending on the renal and postrenal pathology.

CONTINUOUS PROTEINURIA

Continuous proteinuria indicates a relatively advanced stage of renal disease.

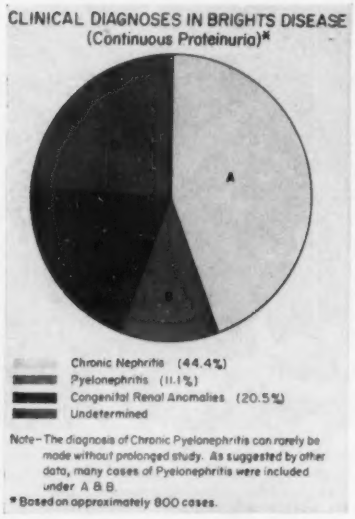


HISTORY IN BRIGHT'S DISEASE (Continuous Proteinuria)

1. More than one-half of the patients in this group had no knowledge of previous renal disease.

2. About one-third gave only history of "albuminuria."

3. Only about 10% gave a definite history of known renal disease and 5% a history of hematuria.


CLINICAL DIAGNOSES IN BRIGHTS DISEASE
(Continuous Proteinuria)*
A
B
Chronic Nephritis (44.4%)
Pyelonephritis (11.1%)
Congenital Renal Anomalies (20.5%)
Undetermined
Note—The diagnosis of Chronic Pyelonephritis can rarely be made without prolonged study. As suggested by other data, many cases of Pyelonephritis were included under A & B.
* Based on approximately 800 cases.

DIAGNOSIS IN BRIGHT'S DISEASE (Continuous Proteinuria)

The relative incidence of clinical diagnoses is indicated. Many undetermined cases were probably pyelonephritis, the diagnosis of which is exceedingly difficult. Some cases in all groups represent a later stage of chronic (orthostatic) proteinuria, previously unrecognized or considered insignificant.

The possibility that chronic proteinuria per se may aggravate renal injury cannot be excluded.

SUMMATION

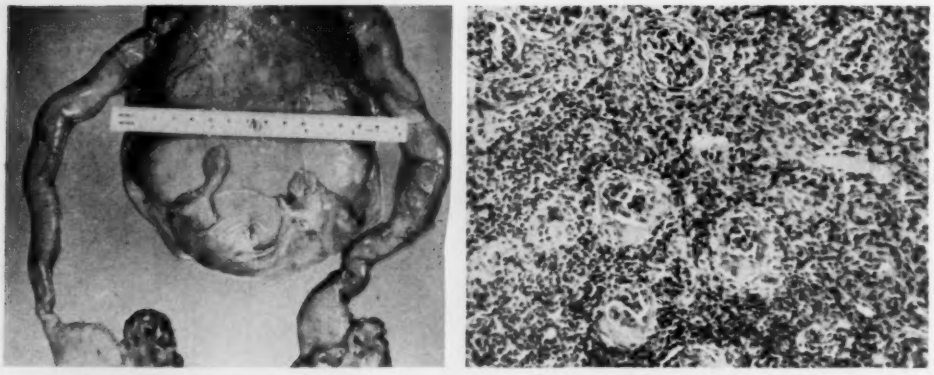
Orthostatic proteinuria is associated with renal disorders which may be neither latent nor benign. Many cases later diagnosed "chronic nephritis" previously masqueraded as orthostatic proteinuria.

A practical accurate method for evaluation and study of patients with proteinuria is reviewed. Chronic proteinuria is classified as intermittent, orthostatic, and continuous.

The frequent discovery of advanced renal disease in apparently normal young adults, on routine examination, is cause for concern.

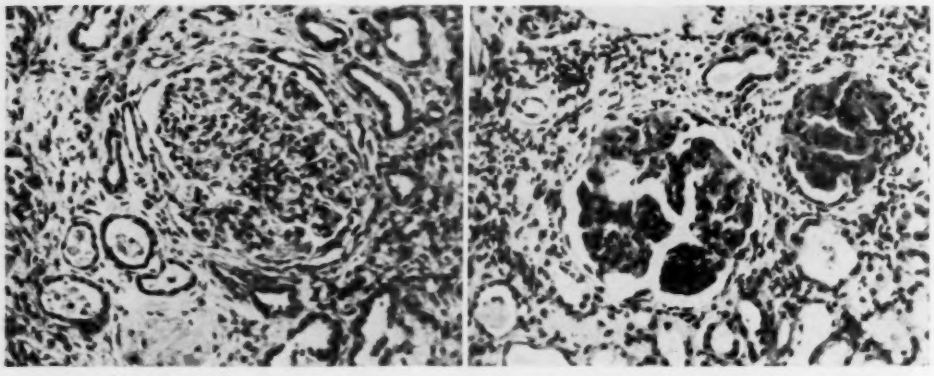
These results are based on experiences at one hospital, serving a fraction of one Army area, and represent only a small proportion of renal disease that may be found in young adult males under the guise of obscure chronic proteinuria.

Obscure chronic proteinurias are common disorders in young persons, which may be related to renal vascular disease of later decades. They are public health and clinical problems, which merit adequate study to properly determine their evolution and significance.



CHRONIC PYELONEPHRITIS

Proteinuria may be inconstant (orthostatic) and pyuria variable in chronic pyelonephritis. Careful urine sediment examination and culture may establish the diagnosis at a stage when therapy can be effective. Later, with hypertension and renal insufficiency, proteinuria becomes constant but rarely intense and may escape detection in very dilute urines. Specimen (left) is from a 22-year-old soldier who died with renal insufficiency on his first hospital admission. Marked parenchymal destruction by inflammatory tissue is shown (right).



THE CONTRACTED KIDNEY

In cases of advanced Bright's disease without prior history, the specific causative disease may escape precise definition by clinician and pathologist. Proteinuria, although constant, may appear mild, owing to dilution by polyuria. The sediment is rarely informative. Clinically it is usually assumed that these are cases of "chronic nephritis." However, other lesions with obscure chronic proteinuria may contribute to this end-stage (left and right).

Many patients with renal insufficiency were unaware of any disease until proteinuria was discovered on routine examination.

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*Roentgenograms and case history courtesy of I. Richard Schwartz, M.D., Kings County Gastrointestinal Clinic, Brooklyn, N. Y.

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(1) Clara, M.: Med. Monatsschr. 7:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

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References: 1. Hodes, M. E.: Clin. Chem. *5*:59 (Aug.) 1953. 2. Wollenweber, H. L.: Current M. Digest *21*:109 (March) 1954. 3. Okatvec, W. A., Jr., and Smetana, E. J.: Tech. Bull. Registry M. Tech. *24*:28 (Jan.) 1954. 4. Oktavec, W. A., Jr., and Smetana, E. J.: Am. J. Clin. Path. *24*:250 (Feb.) 1954.

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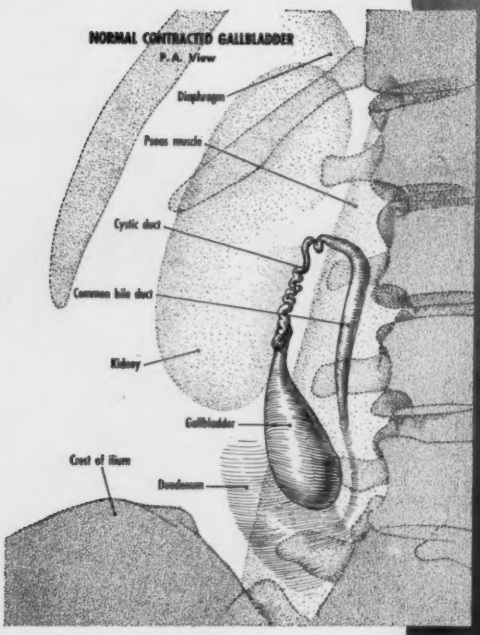

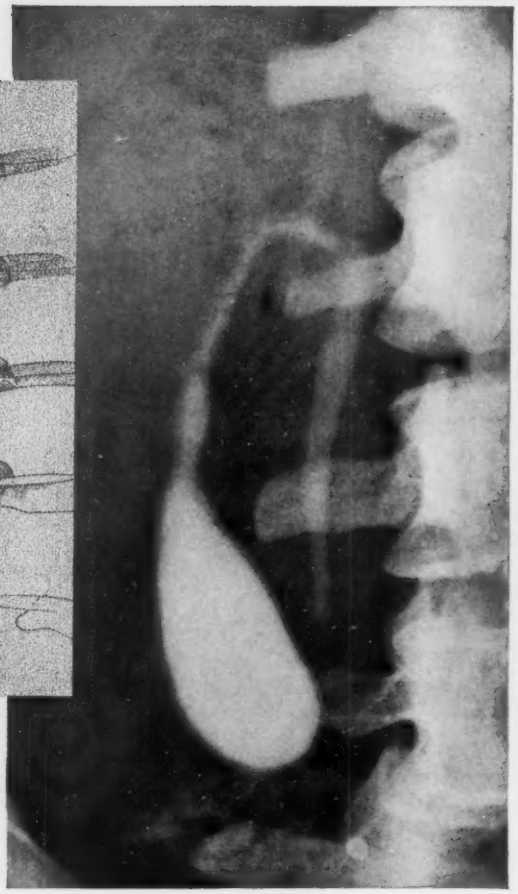

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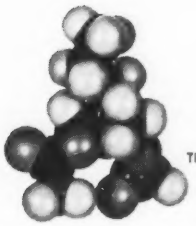

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